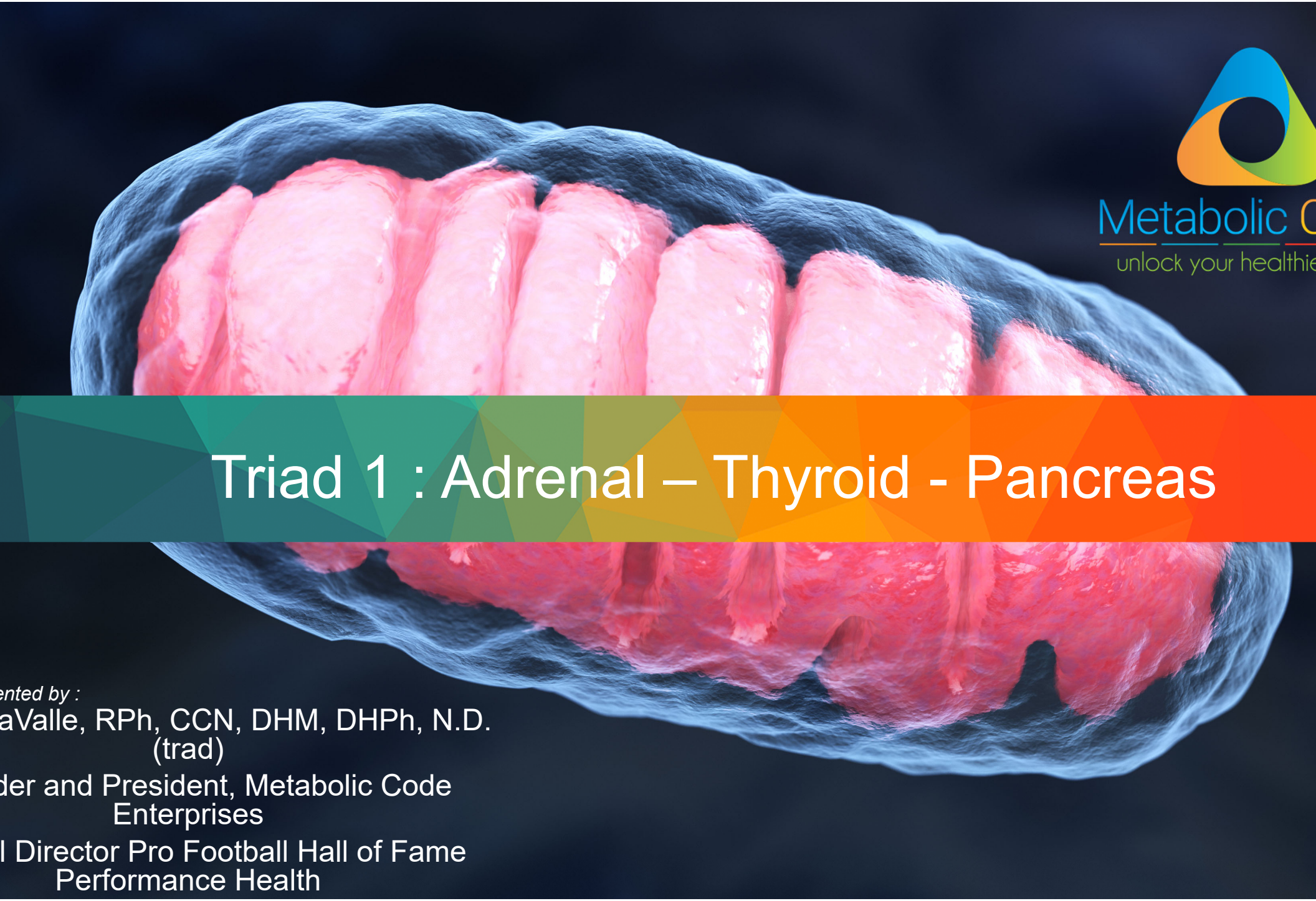


Triad 1 : Adrenal – Thyroid - Pancreas

ented by :
aValle, RPh, CCN, DHM, DHPh, N.D.
(trad)
der and President, Metabolic Code
Enterprises
l Director Pro Football Hall of Fame
Performance Health

This material is provided for educational and informational purposes only to licensed health care professionals. This information is obtained from sources believed to be reliable, but its accuracy cannot be guaranteed. Herbs and other natural substances are very powerful and can occasionally cause dangerous allergic reactions in a small percentage of the population. Licensed health care professionals should rely on sound professional judgment when recommending herbs and natural medicines to specific individuals. Individual use of herbs and natural medicines should be supervised by an appropriate health care professional. The use of any specific product should always be in accordance with the manufacturer's directions.

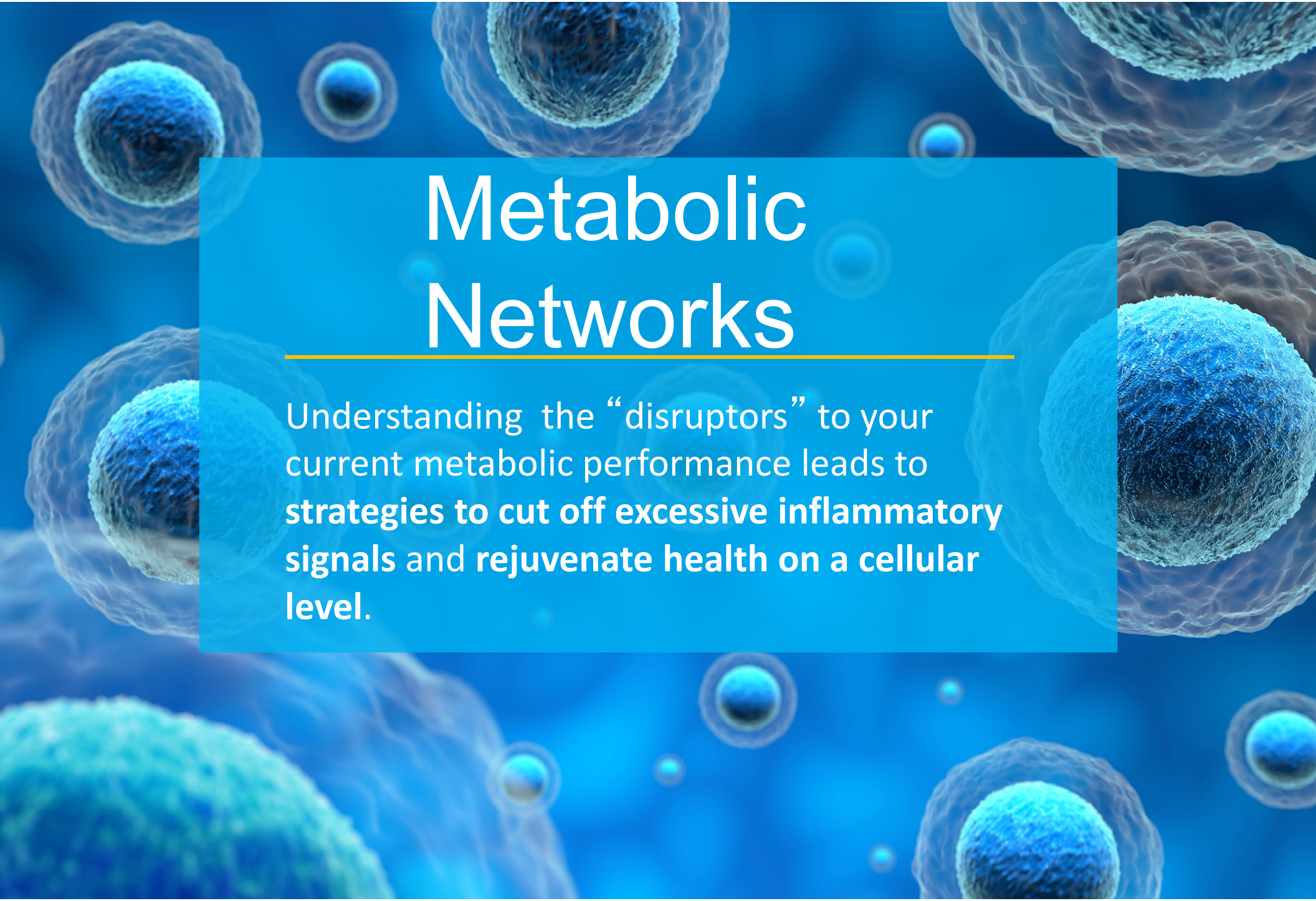
METABOLISM

he sum total of all the chemical
eactions **driving how you feel today**
nd creating the chemistry
noving you toward future health.

METABOLISM

rectly under the influence of Global
Metabolic Inflammatory Signaling =

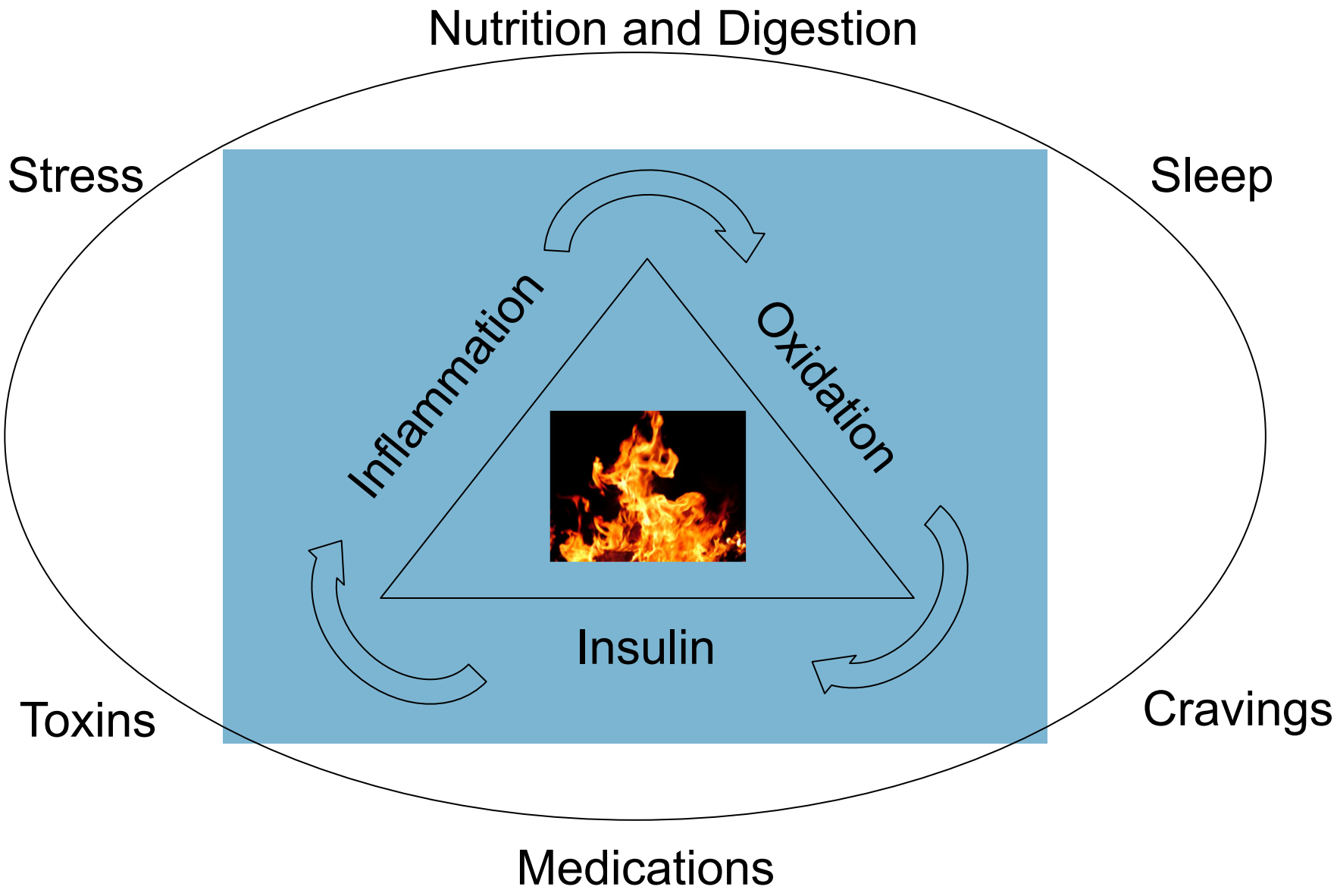
Metaflammation drives
Metabolic Dysregulation


Metabolic Networks
Understanding the “disruptors” to your current metabolic performance leads to **strategies to cut off excessive inflammatory signals** and **rejuvenate health on a cellular level**.

Key Tenants of

Aging, Performance and Vitality

- Oxidative Stress / Inflammation
- Hormonal Balance
- Stress Hormones
- Glucose / Insulin Regulation
- GUT integrity and microbiome diversit
- Immune Balance
- Environmental Burden
- Individuality


Nutrition and Digestion
Stress
Sleep
Inflammation
Oxidation
Insulin
Toxins
Cravings
Medications

Lifestyle and Metabolic Influencers

OVER TIME

Your Health and How You Feel

At the core of Metabolic Dysregulation is

METAFLAMMATION

CDC, www.cdc.gov Accessed

Metaflammation

AKA "Inflammaging" and Metabolism Induced Inflammation

Chronic low-grade inflammatory sequela

Increases aging processes and metabolic signaling issues

Characterized by elevated levels of blood inflammatory markers

- CRP
- HCY
- ESR
- oxLDL
- IL-6
- TGF-beta1
- TNF-alpha
- Others

Prattichizzo F, et al. Inflammageing and metaflammation: the yin of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

Metaflammation/ Inflammaging

- Prominent in most aging individuals

- ↑ susceptibility to:
  - Chronic morbidity
  - Disability
  - Frailty
  - Premature death

Ferrucci L, et al. Inflammaging: chronic inflammation in ageing, cardiovascular disease and frailty. Nat Rev Cardiol. 2018;15(9):505-522.

Metaflammation/ Inflammaging Causative Factor

- Genetic susceptibility
- Chronic cortisol release – HPA imbalance
- Central obesity
- Increased gut permeability
- ↓ Microbiome diversity
- Cellular senescence
- NLRP3 inflammasome activation
- SIRT1 dysregulation
- ↑ Oxidative stress
- ↑ Mitochondrial dysfunction
- Immune cell dysregulation – T helper imbalances
- Chronic infections

Ferrucci L, et al. Inflammaging: chr
inflammation in ageing, cardiovascu
disease and frailty. Nat Rev Cardiol
2018;15(9):505-522.

Metaflammation Major Contributors

- **Stress – cortisol**
  - Activates inflammatory processes in brain and peripherally
- GUT health
  - Microbiota alterations
  - LPS release
  - Low grade endotoxemia
- Obesity

ncrease inflammatory compounds “adipokines”

Liu Y, et al. Inflammation: The common pathway of stress-related diseases. Front Hum Neurosci. 2017;11:316.

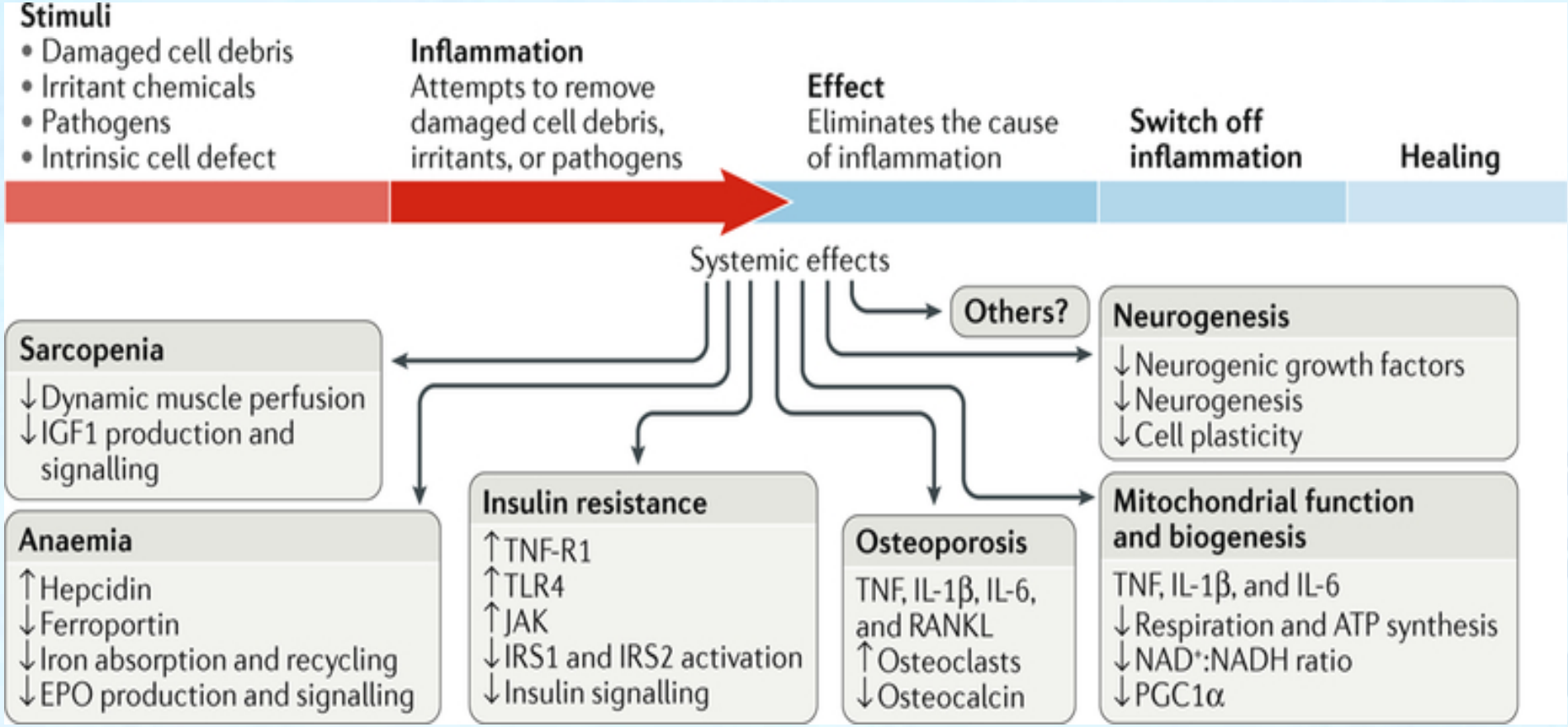
Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:

Metaflammation Major Contributors

- DIETARY FACTORS
  - Western Diet
    - High sugar; refined carbs
    - High fat - trans and saturated fats
    - Salt
    - Artificial additives; sweeteners, dyes, preservatives
    - Low in fiber, complex carbs, nutrients
- Liver / Kidney issues also lead to metaflammation
- DIND and DIMD

Liu Y, et al. Inflammation: The common pathway of stress-related diseases. Front Hum Neurosci. 2017;11:316.
Christ A, et al. The western lifestyle has lasting effects on metaflammation. Nature Rev. 2019;19:267-68.

Metaflammation Induces Catabolic S



Ferruci L, et al. Inflammageing: chronic inflammation in ageing, cardiovascular disease and frailty. Nat Rev Cardiol. 2018;15(9):505-22.

Drug-Induced Nutrient Depletions (DINDs)

Drugs can inhibit nutrient absorption, synthesis, transport, storage, metabolism, or excretion

Health problems are multi-factorial & complex

Tremendous opportunity to improve health outcomes and reduce risk of polypharmacy and adverse events.

Pharmacists are 1st Responders for DIND intervention

Write down these numbers

- How many people come into your practice that are on:
- Statins
- H2 Blockers and PPI's
- Diabetes Med's
- Metformin
- Blood Pressure medication including Diuretics
- Anxiety and Sleep disturbances

- ALL DEPLETE KEY NUTRIENTS

Drug-Induced Nutrient Depletion Examples

Oral Contraceptives/Hormones:	FA, B6, B1, B2, B3, B12, C, E Mg, Se, Zn, tyrosine, CoQ10,
Anticonvulsants:	Biotin, D, B1, B6, B12, K,FA, Ca
Metformin:	CoQ10, B12 FA
Beta-blockers:	B6, CoQ10, Ca, Mg, K, Zn,
NSAIDs:	FA, melatonin, zinc, DHEA,
Corticosteroids:	Ca, CoQ10, DHEA, FA, Mag, D, K, B6, B12, Se, C, E, Cr, Zn
Statins:	CoQ10, D, testosterone, E, carnitine, Omega-3s, Zn, Se, Cu, K2metop
Beta-blockers:	CoQ10, melatonin, testosterone
PPIs	Ca, FA, Fe, C, D, B12, Mag, Zn
Benzodiazepines:	Melatonin
Opioids:	DHEA, Testosterone, Melatonin

Stress-Induced Nutrient Depletions

- Magnesium
- Iron
- Zinc
- Vitamin D
- Calcium
- B vitamins – B3

Stressed Patients also Taking Benzodiazepines = DIND

More than 1 in 8 people have use a benzodiazepine in the past year (12.6% of population in US)

Benzodiazepines reported to deplete:

- **Melatonin**

Natural sleep hormone - antioxidant

Levels decrease with aging

Decreases with stress, hormonal imbalances

Improves circadian insulin production

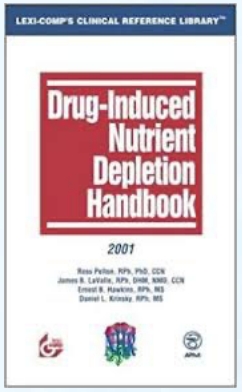
3-20mg (can use SR for part of dosage)

Wakabayashi H, et al. Effect o
psychotropic drugs on the con
melatonin, serotonin and N-
acetylserotonin in rat pineal gl
Jpn J Pharmacol.1989
Feb;49(2):225-34.

Melatonin DIND – Drug-Induced Nutrient Depletion

elatonin is reported to be depleted by:

- Beta-blockers
- Calcium channel blockers
- Benzodiazepines
- Estrogen-containing medications
- Hydralazine
- Loop diuretics
- Theophylline
- Antidepressants, including SSRI (Selective serotonin reuptake inhibitors
- NSAIDs (Non-steroidal anti-inflammatory drugs)

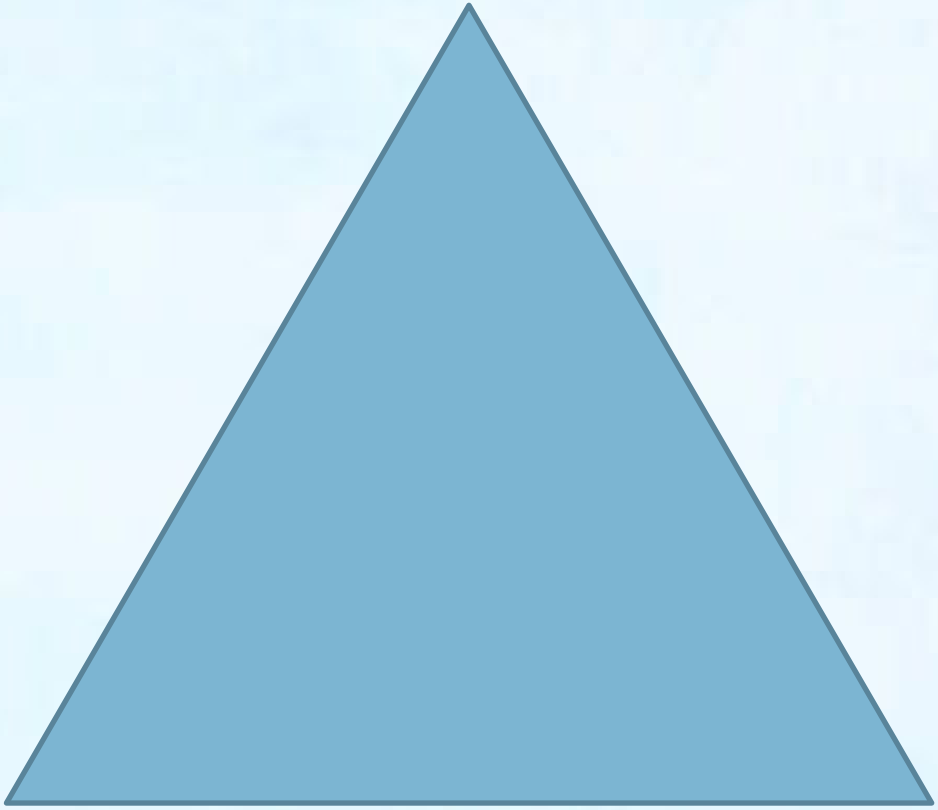


LaValle JB, Pelton R et al. Drug Induced Nutrient Depletion Handbook. 2001. LexiComp Publishing, Hudson, OH.

TRIAD 1

- Energy production and circulation
- Stress-metabolism-sugar
- Central regulator of physiology
- Normal: vitality and wellbeing
- Imbalanced: fatigue and obesity

Thyroid -
Metabolism



Pancreas –
Sugar

Adrenals -
Stress

Triad 1: Characteristics

- Balance
- Movement
- Energy
- Rhythmicity
- Vitality
- Spirituality

Cortisol – Stress and the Impact on Metabolic Homeostasis

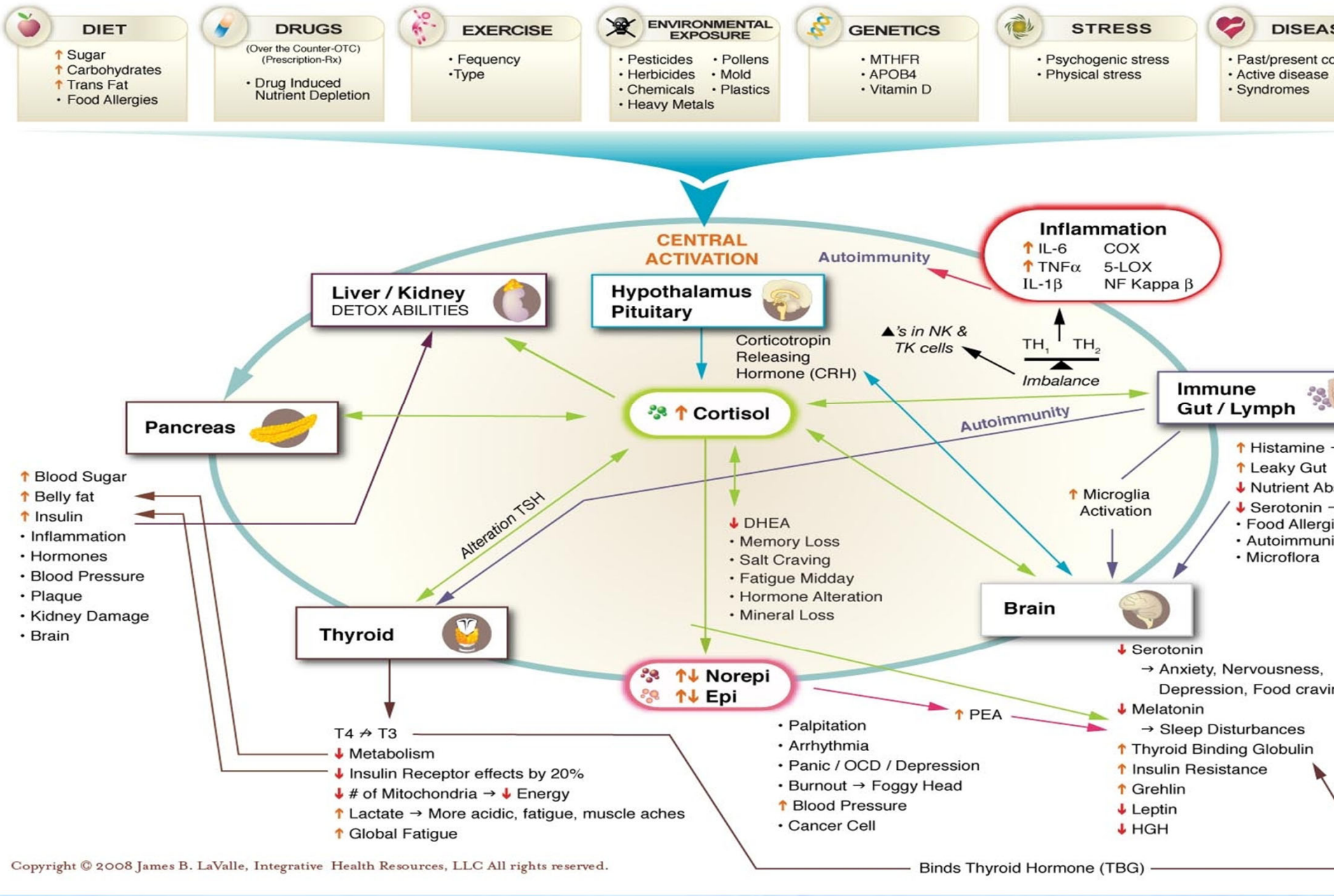


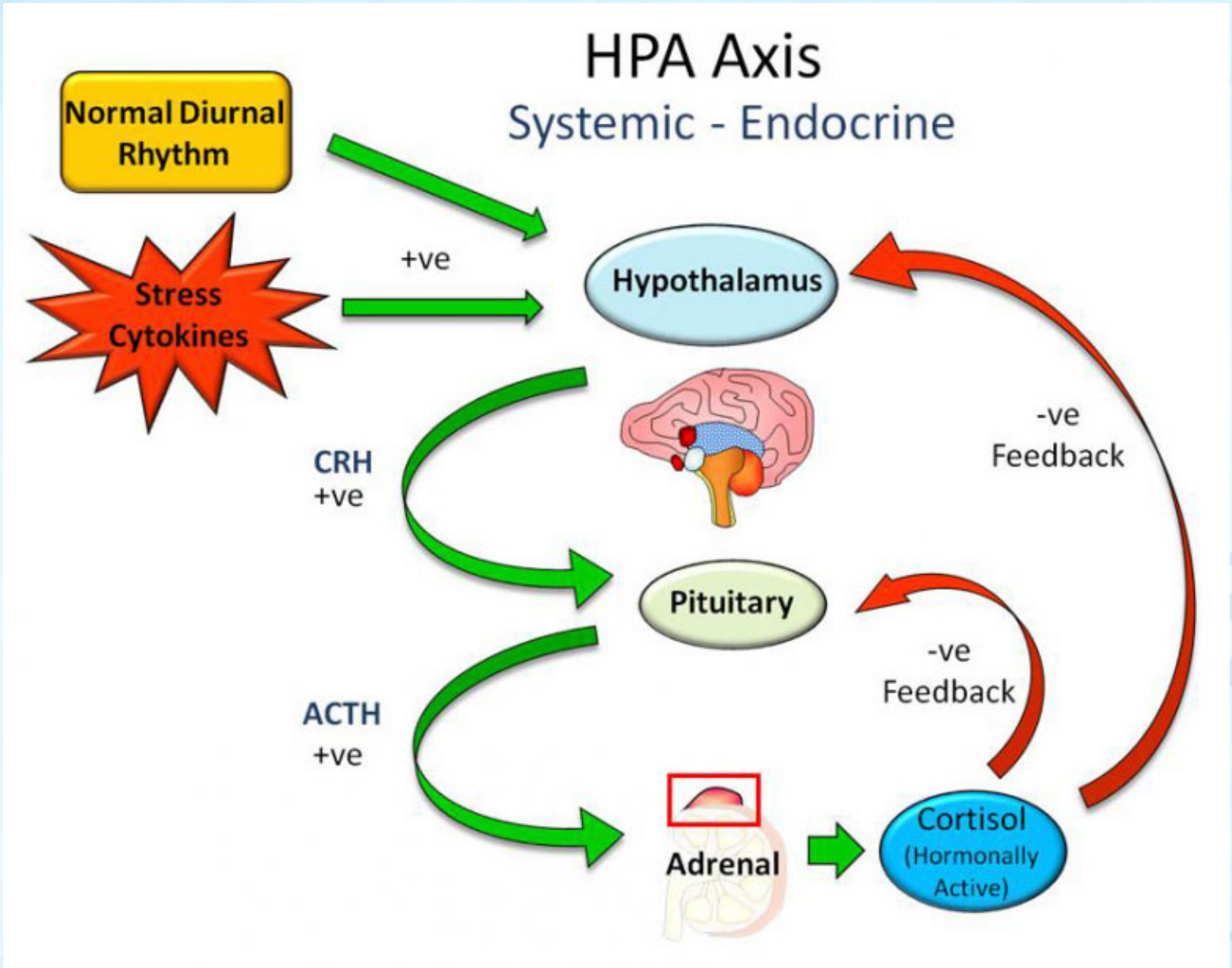


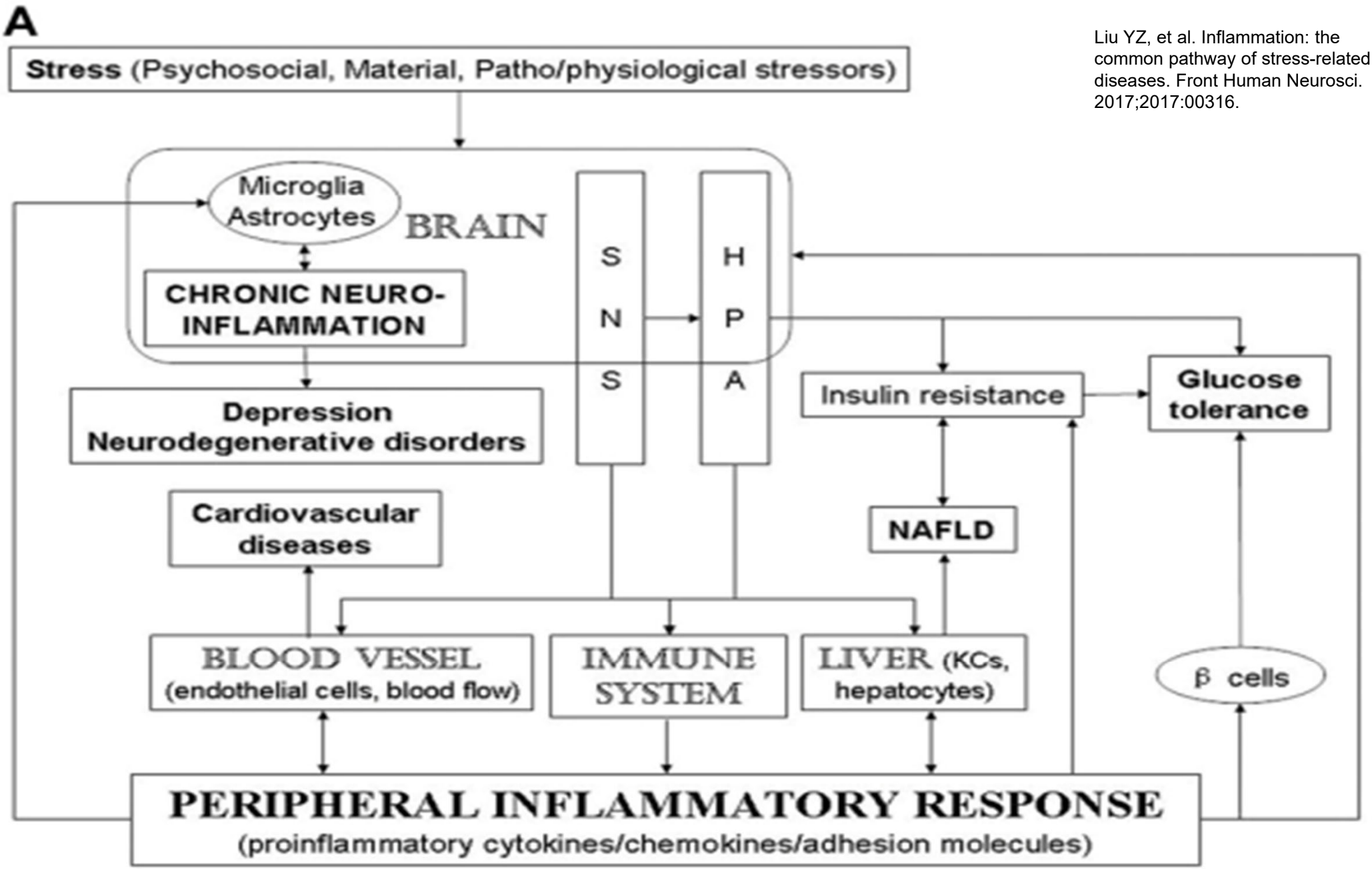





Metabolic Activation Pathways

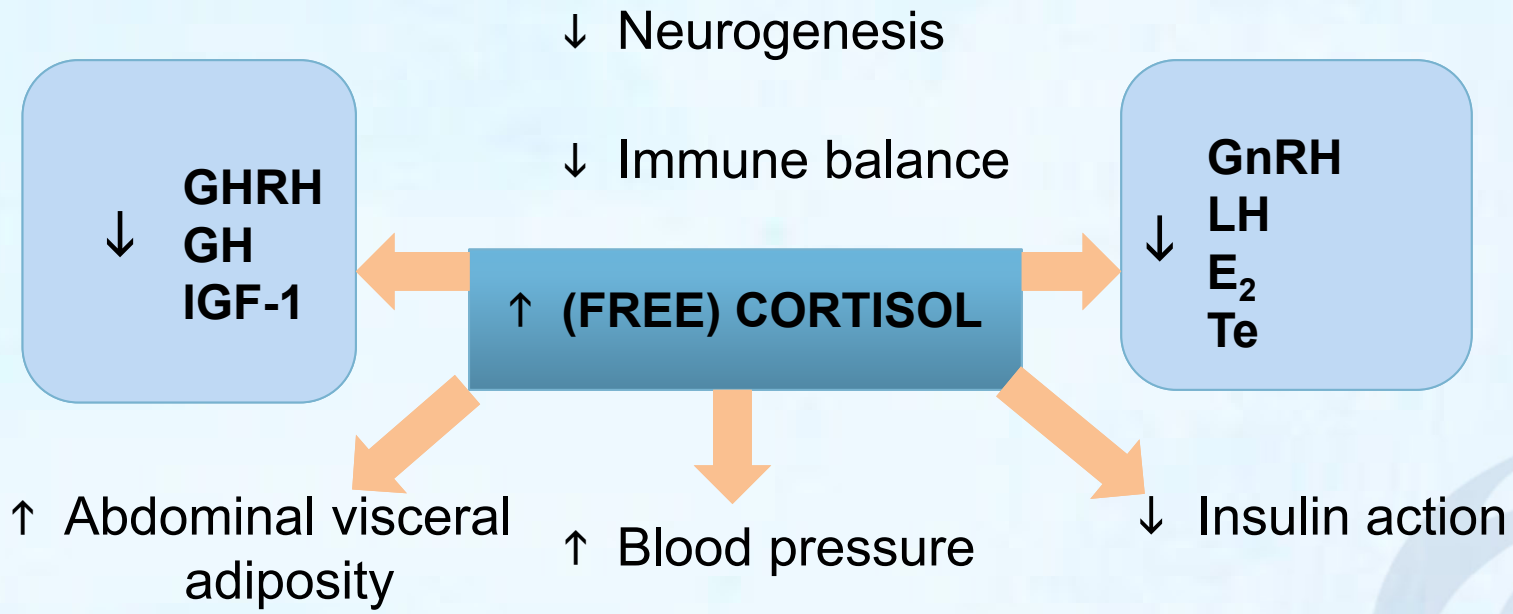



HPA Axis
Systemic - Endocrine
Normal Diurnal Rhythm
Stress Cytokines
+ve
Hypothalamus
CRH
+ve
-ve
Feedback
Pituitary
ACTH
+ve
-ve
Feedback
Adrenal
Cortisol
(Hormonally Active)



Liu YZ, et al. Inflammation: the common pathway of stress-related diseases. Front Human Neurosci. 2017;2017:00316.

Clinical Effects of Excessive HPA axis Activation



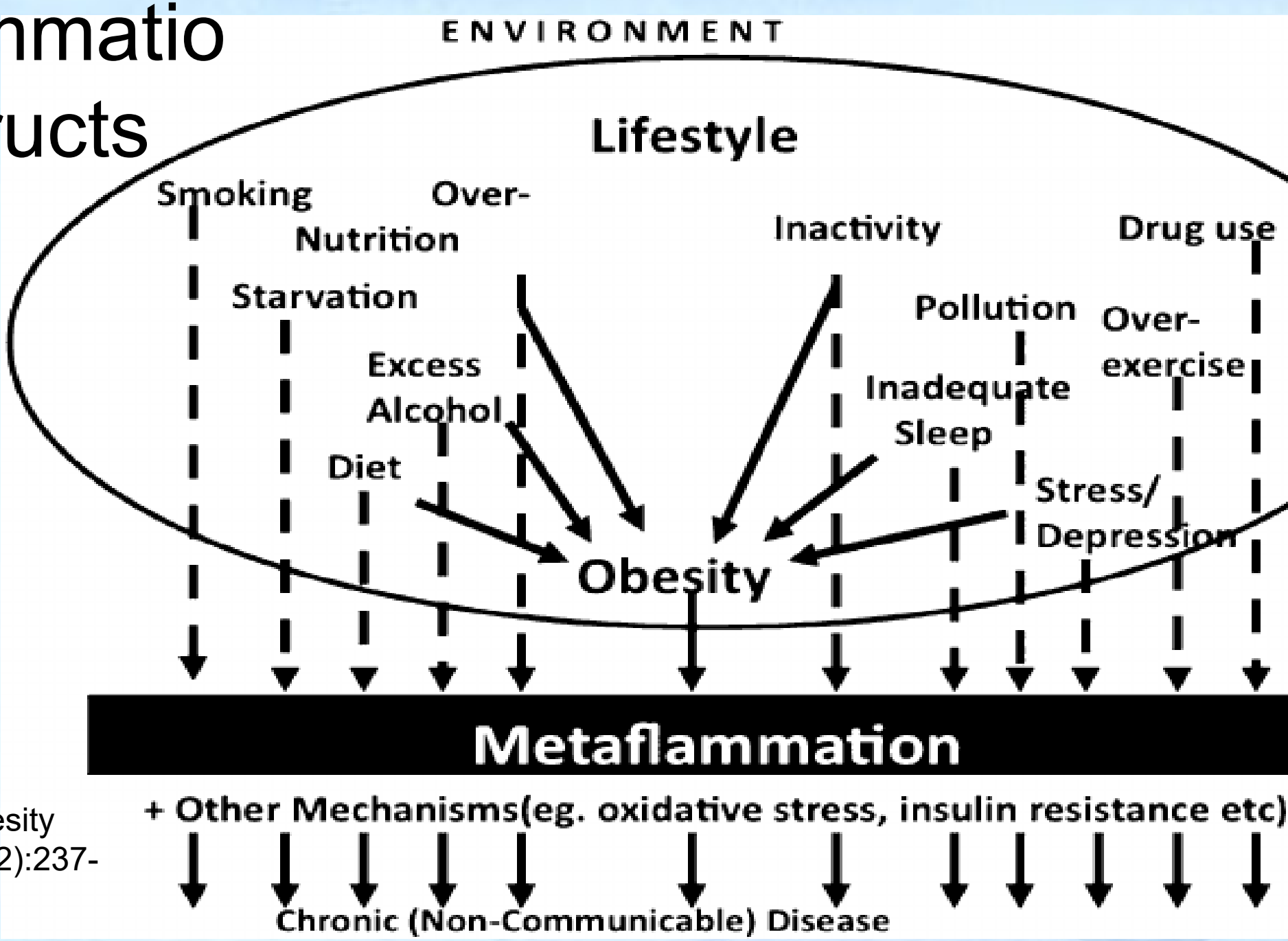
OUTCOMES

(osteopenia, sarcopenia, syndrome X, cognitive decline, immunological compromise)

(fractures, frailty, cardiovascular disease, memory loss, infectious complications)

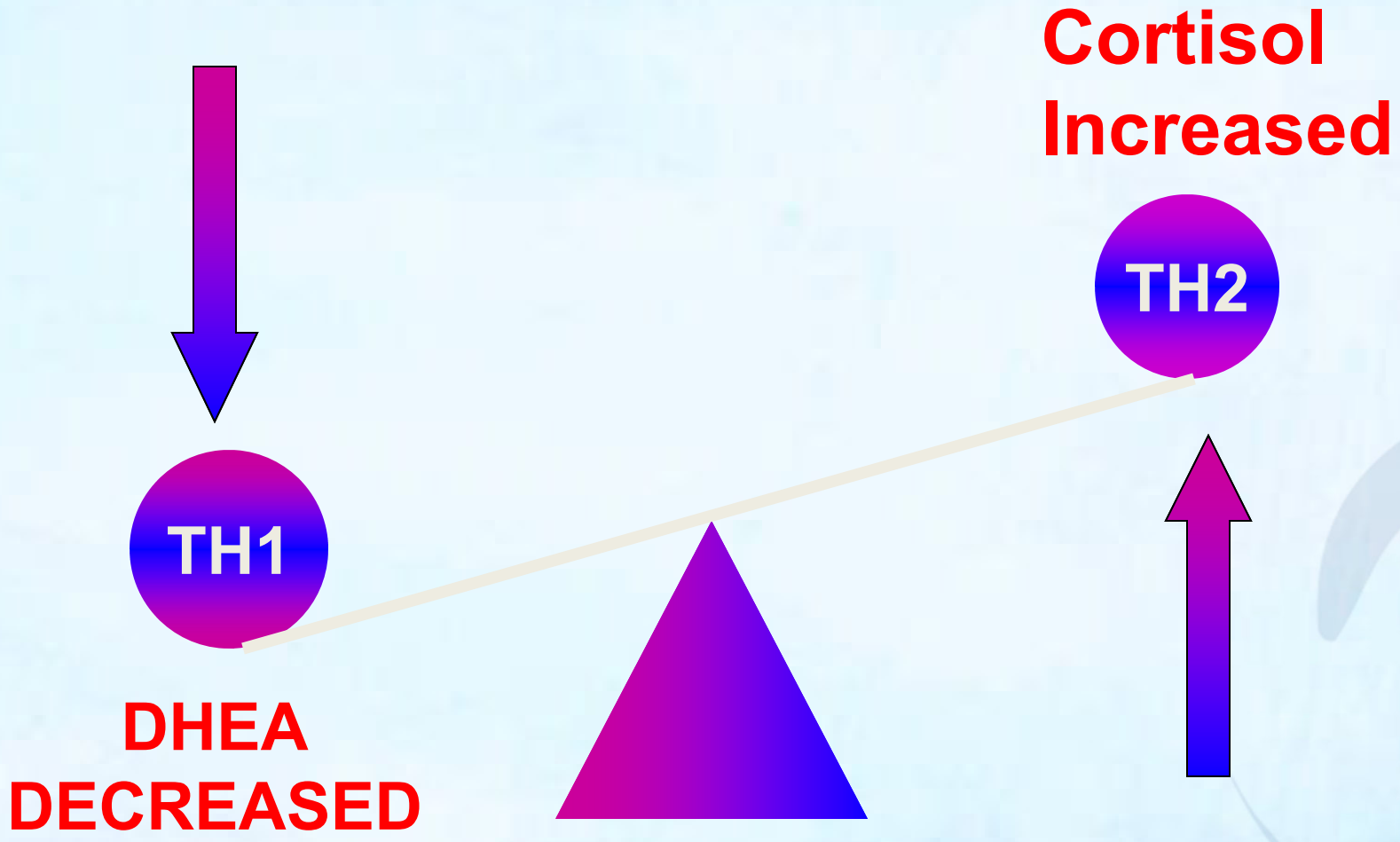
Adapted from: Endocrinology and Metabolism Clinics of North America, Elsevier Publishing, ed. Anne R. Cappola. June 2013, vol. 42, no. 2.

aflammatio
onstructs



G, et al. Obesity
s. 2008;10(2):237-

IMBALANCE=DISEASE



Allostatic Load

- Wear and tear of body and brain
- Results from chronic over activity or inactivity of body systems normally involved in environmental challenge and adaptation
- **Allostatic load** results when HPA axis is either overworked or fails to shut off after stressful events
- Also when normal compensatory systems over-react

Fries et al. *Psychoneuroendocrinology*. 2005;30(10):1010-1016

Metabolic Effects of Chronic Cortisol Elevati

Increased insulin secretion

Increased fat deposition

Alteration in immune function

Muscle wasting

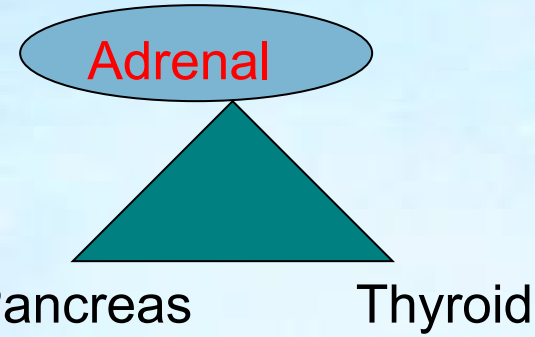
Hypothyroidism (adrenal exhaustion)

Memory loss

Alteration in sex hormones

Mental and Emotional instability

- Bone loss/mineral loss
- Sodium and water retention
- Elevated blood lipids
- Loss of REM sleep
- Increase plaque formation
- Increase in cardiovascular risk factors
- Receptor Site activation on Tumor cells



Adrenal Glands

Chronic Stress
Cortisol Levels Increase

Serotonin Levels

- •Depression/Anxiety
- •Cravings for Sugar and Carbohydrates
- •Feeling flat

DHEA Levels

- •Now Focused on Stress
- •Sex Drive drops-changes making testosterone, Progesterone, etc.

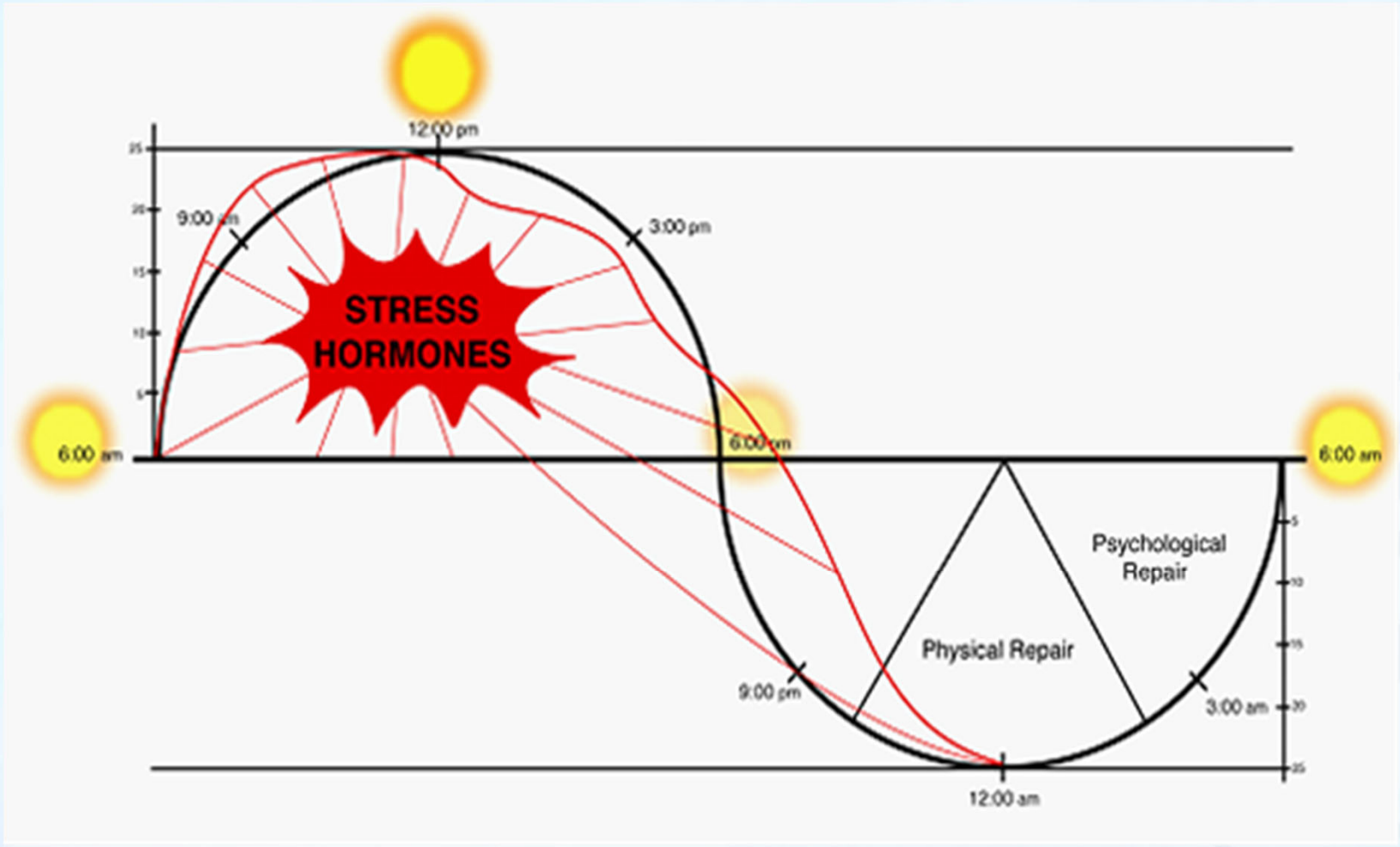
Melatonin Levels

- Lose/Can't Sleep
- Lose Energy
- Increase cravings for comfort food

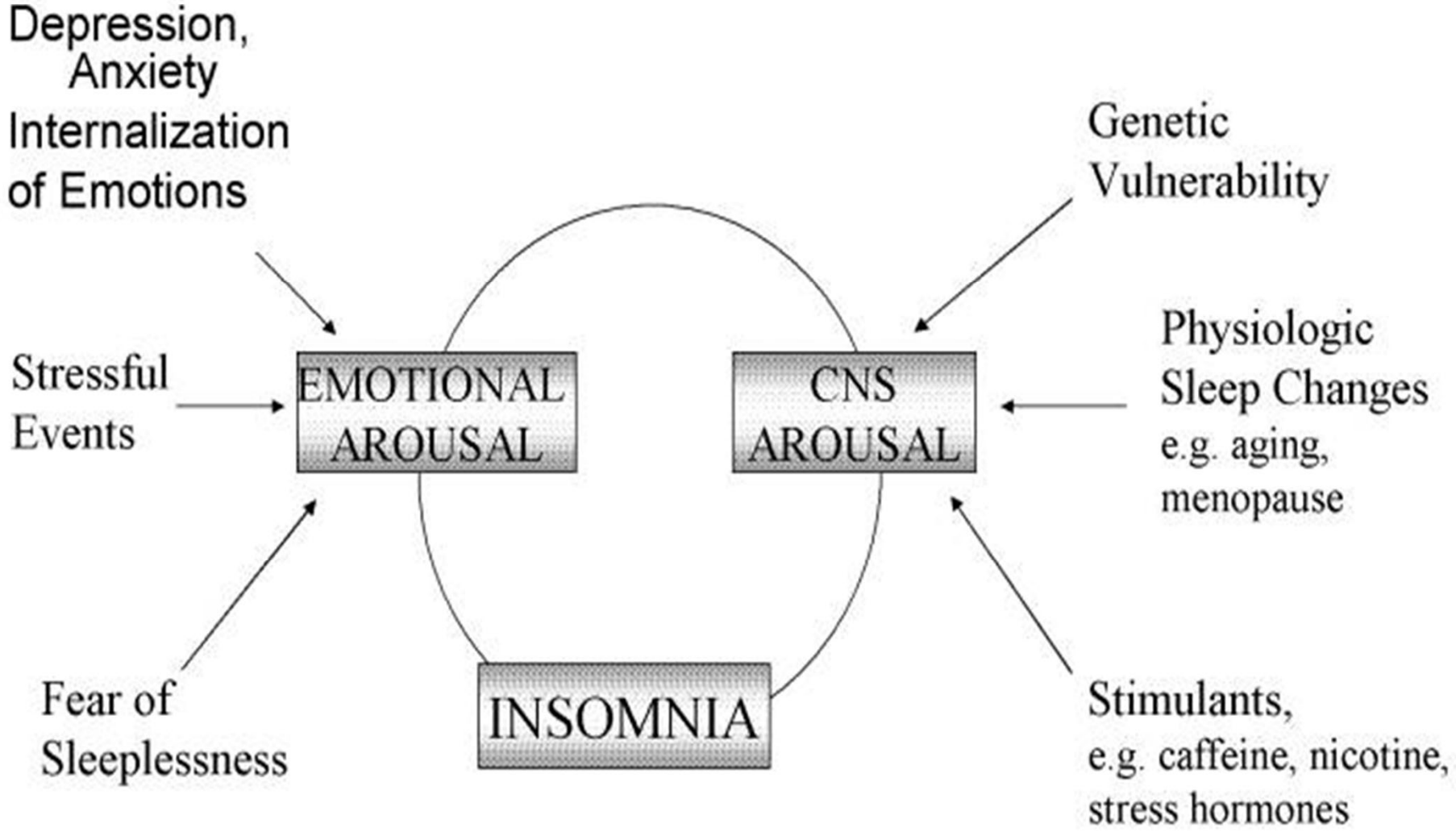
Cortisol and Sleep

- Cortisol release is controlled in slow-wave sleep by decreases in corticotropin-releasing hormone (CRH) and increases in growth hormone (GH)
- Exposure to chronic stressors imbalances HPA axis and disrupts normal diurnal pattern of GH, CRH and ACTH release
- Results in a paradoxical rise in cortisol in evening hours and initial sleep phases
- *Nocturnal hypercortisolism* can lead to sleep fragmentation, increasing cortisol even more

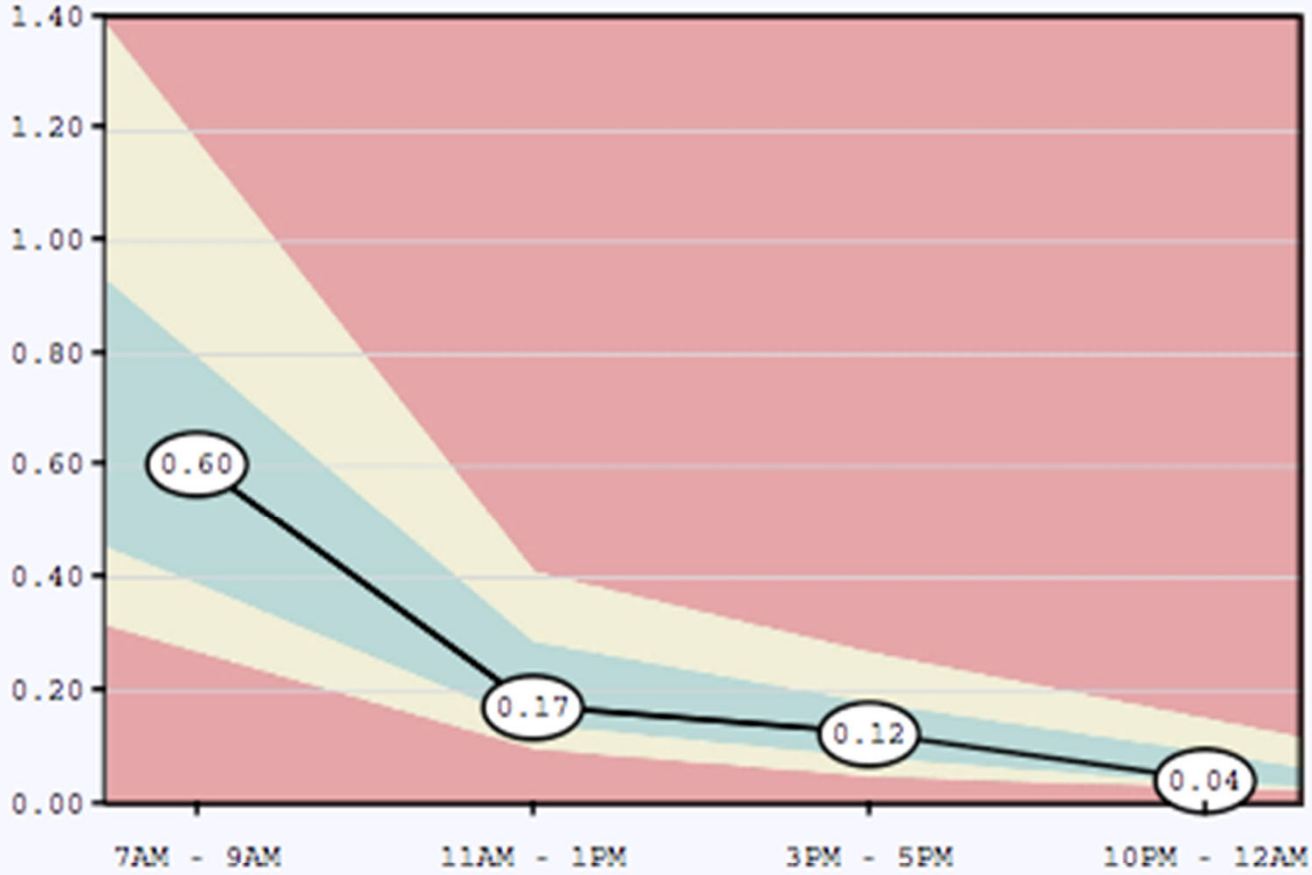
Normal Diurnal Hormone Release



Hyperarousal Hypothesis (Emotional and Physiological)



Salivary Cortisol and DHEA



Cortisol

Reference Range

1 Hour After Rising
7AM - 9AM:

0.27-1.18 mcg/dL

11AM - 1PM:

0.10-0.41 mcg/dL

3PM - 5PM:

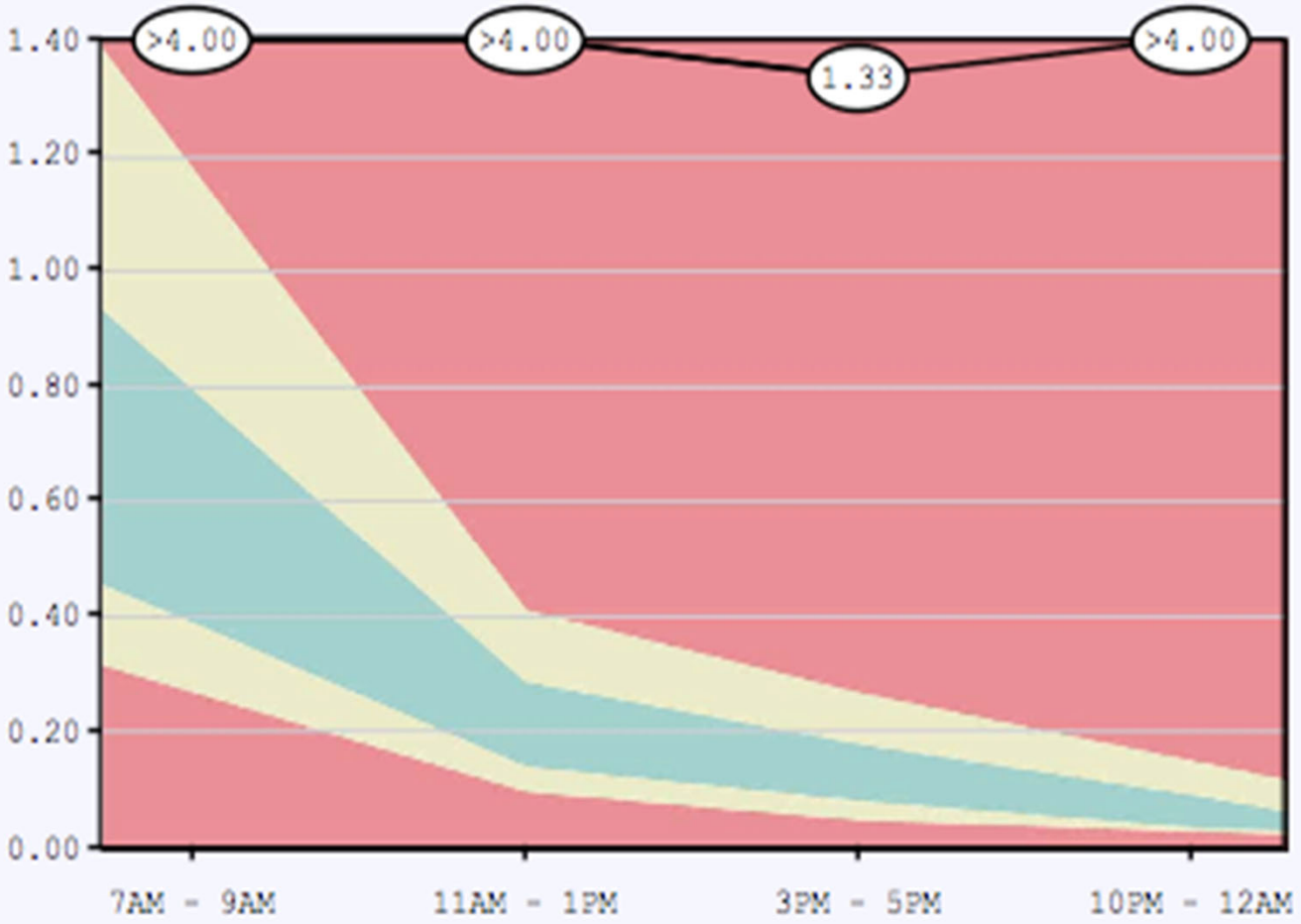
0.05-0.27 mcg/dL

10PM - 12AM:

0.03-0.14 mcg/dL

Hormone	Reference Range	Reference Range
DHEA 7am - 9am	297	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	495	115-1,188

Salivary Cortisol and DHEA



Cortisol•

Reference Range

1 Hour After Rising
7AM - 9AM:

0.27-1.18 mcg/dL

11AM - 1PM:

0.10-0.41 mcg/dL

3PM - 5PM:

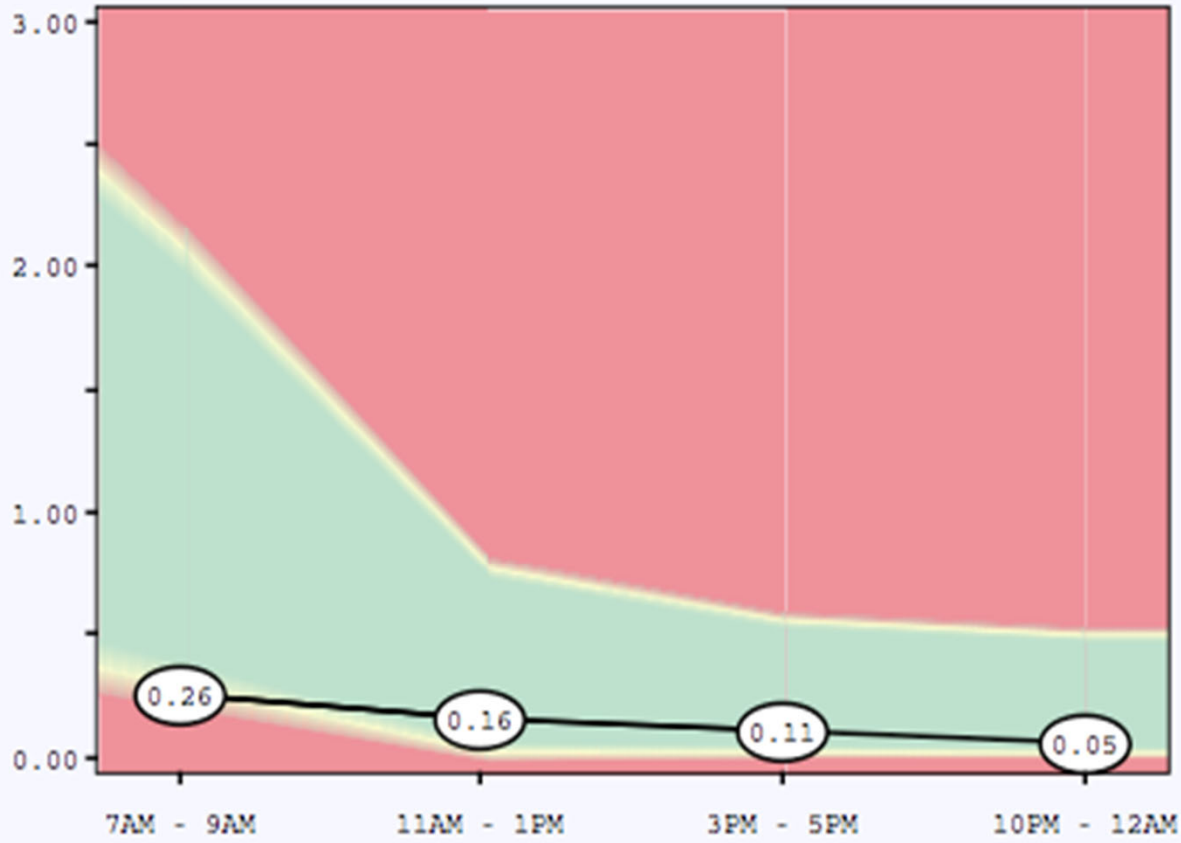
0.05-0.27 mcg/dL

10PM - 12AM:

0.03-0.14 mcg/dL

Hormone	Reference Range	Reference Range
DHEA 7am - 9am	191	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	NR	115-1,188

Salivary Cortisol and DHEA



Cortisol

Reference Range

1 Hour After Rising
7AM - 9AM:

0.27-2.06 mcg/dL

11AM - 1PM:

0.03-0.77 mcg/dL

3PM - 5PM:

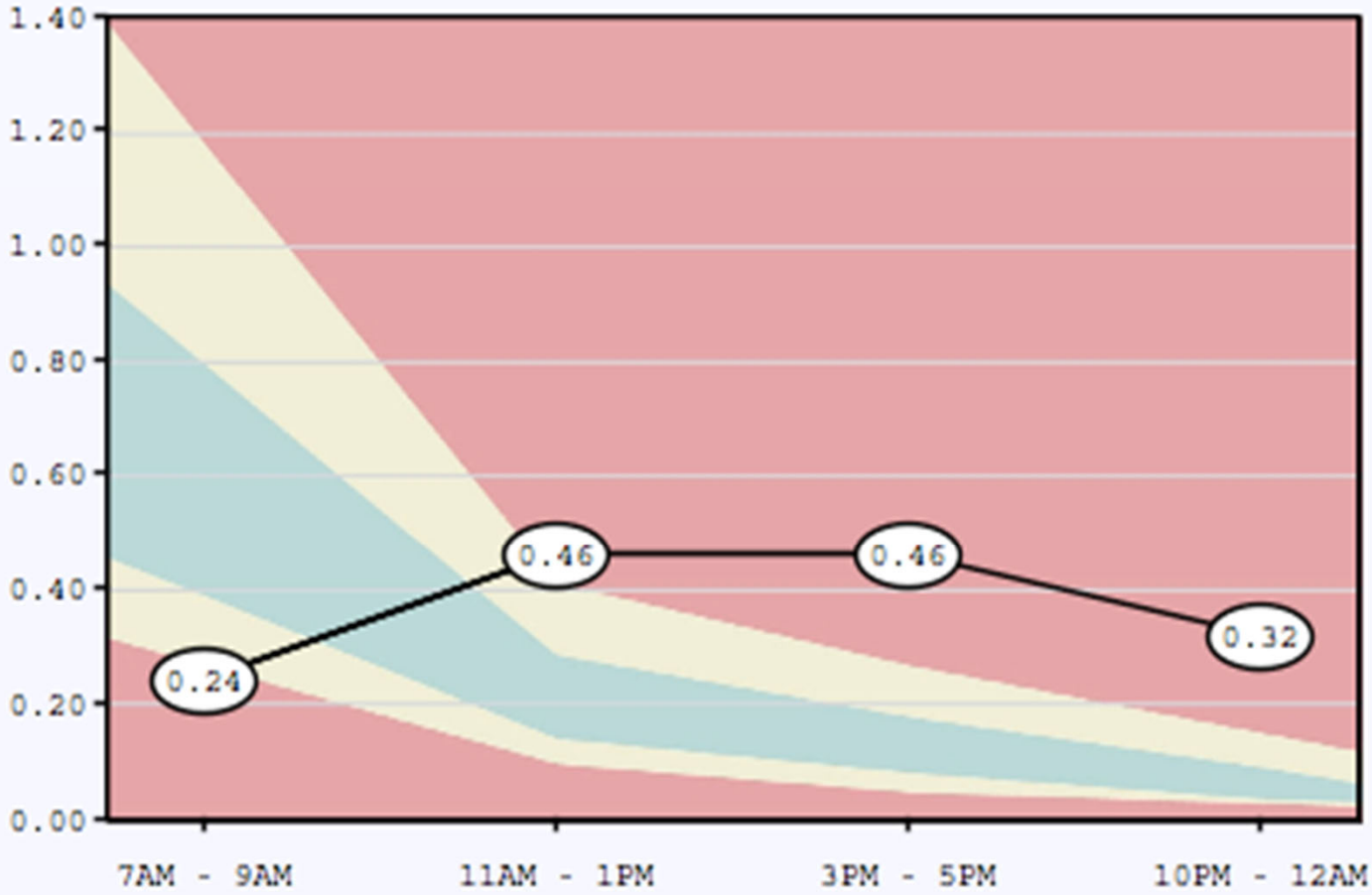
0.03-0.56 mcg/dL

10PM - 12AM:

0.03-0.50 mcg/dL

Hormone	Reference Range	Reference Range
DHEA 7am - 9am	72	14-277 pg/mL
DHEA / Cortisol Ratio x 10,000	277	35-435

Salivary Cortisol and DHEA



Cortisol◆

Reference Range

1 Hour After Rising
7AM - 9AM:

0.27-1.18 mcg/dL

11AM - 1PM:

0.10-0.41 mcg/dL

3PM - 5PM:

0.05-0.27 mcg/dL

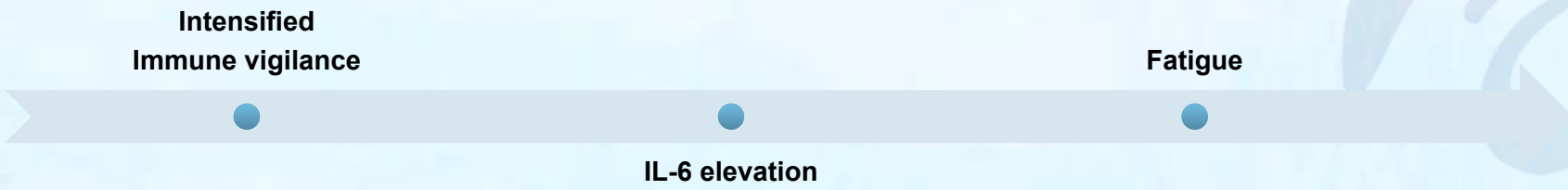
10PM - 12AM:

0.03-0.14 mcg/dL

Hormone	Reference Range	Reference Range
DHEA 7am - 9am	164	71-640 pg/mL
DHEA: Cortisol Ratio/10,000	683	115-1,188

Significance in the Circadian Rhythm

- Flattening the cortisol curve
  - Most predictive of stress related symptoms
  - Most well studied
  - Cortisol levels are up to 30% higher in endurance athletes.
  - Cortisol can lead alterations lead to:



Cortisol and Cardiovascular Disease

- 2006 CARDIA study (n=718, av. Age 40)
- Results – the quartile with the flattest diurnal cortisol slopes were approximately 3 & 1/3 times more likely to have coronary calcification
- Results independent upon socioeconomic status and established cardiovascular risk factors

Matthews K, et al. Diurnal cortisol decline is related to coronary calcifications: CARDIA Study. Psychosom Med. 2006;68:657-661.

HPA axis:Cortisol and Cholesterol Metabolism

- Chronic stress and elevated cortisol are correlated with cholesterol imbalances
  - Decreased HDL
  - Increased triglycerides
  - Increased total cholesterol
  - Increased ox-LDL

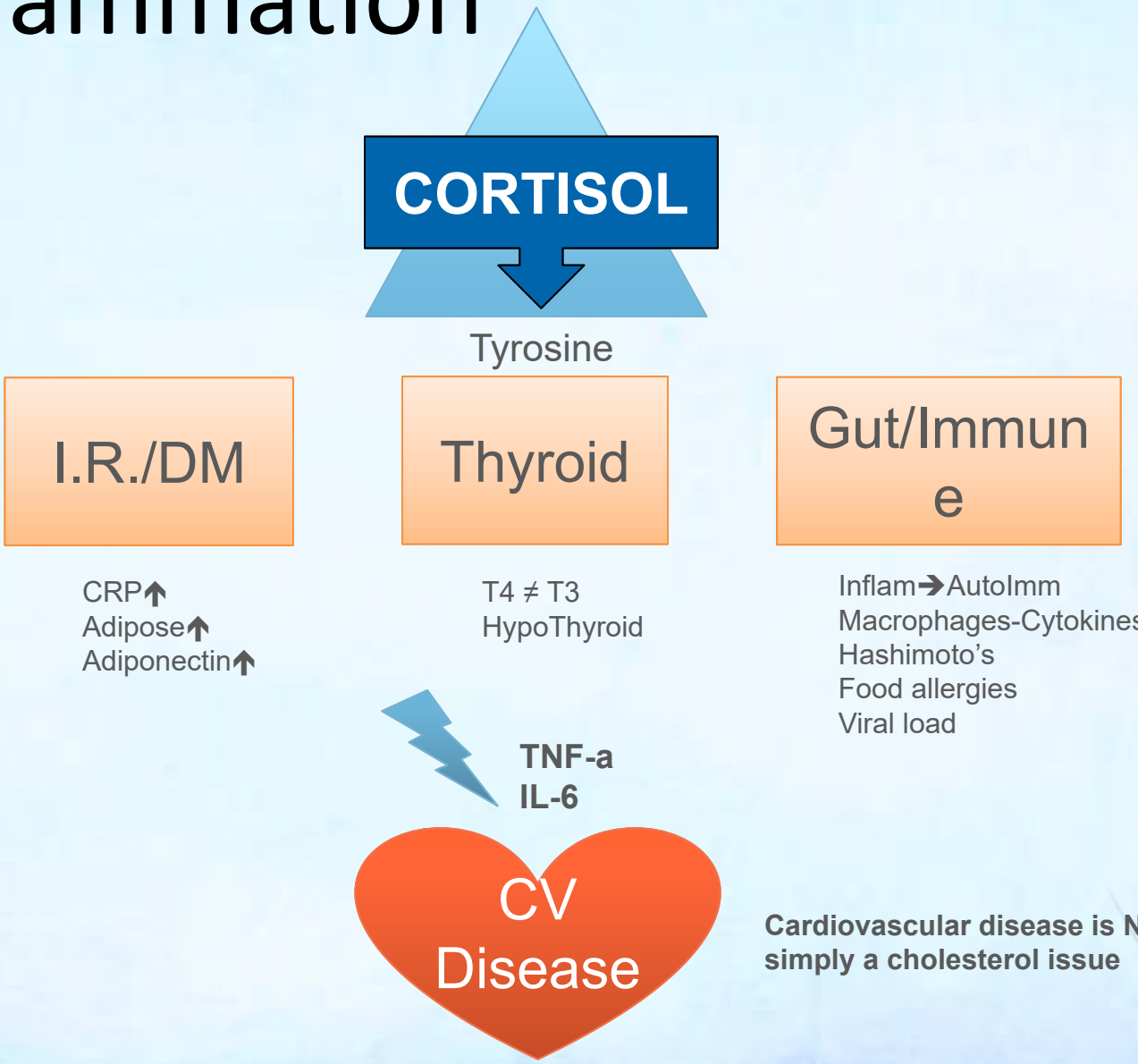
Rosmond R, et al. The hypothalamic-pituitary-adrenal axis activates as a predictor of cardiovascualr disease, type 2 diabetes and stroke. J Intern Med. 2000;247(2):188-97.

Cortisol and Metabolic Syndrome (MetS)

- 2013 clinical study (n=1258 aged 16-64)
- Hair cortisol analyzed
- A higher prevalence of MetS reported in those with elevated long-term cortisol secretion

Stalder T, et al. Cortisol in hair and the metabolic syndrome. J Clin Endocrinol Metab. 2013;98(6):2573-80.

Inflammation



Cardiovascular disease is NOT simply a cholesterol issue

Cortisol and Bone Health

Cortisol Bone Loss

- Clinical study (n=43) men ages 20-59
- 27 male cyclists (non-weight bearing) and 16 runners (weight bearing)
- Results – cyclists had significantly lower bone mineral density vs. runners
- Cyclists 7x more likely to develop osteopenia of the spine

Rector RS, et al. Participation in road cycling vs running is associated with lower bone mineral density in men. Metabolism. 2008;57(2):226-32.

Cortisol and Stress Fractures

- Cortisol reported to imbalance acid/base regulation – lactate ↑
- Exacerbation of acid-induced net calcium efflux from bone
- Decreased bone mineral density
- Functional vitamin D deficiency also reported to be correlated with acute stress

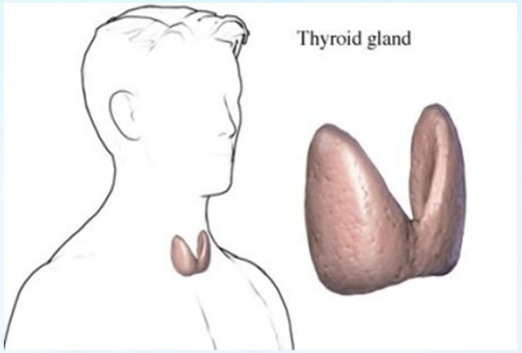
Lee P. Vitamin D metabolism and deficiency in critical illness. Best Pract Res Clin Endocrinol Metab. 2011;25(5):769-81.
Boling EP. Secondary osteoporosis: underlying disease and the risk for glycocorticoid-induced osteoporosis. Clin Ther. 2004;26(1):1-14.

Cortisol and Cognitive Dysfunction

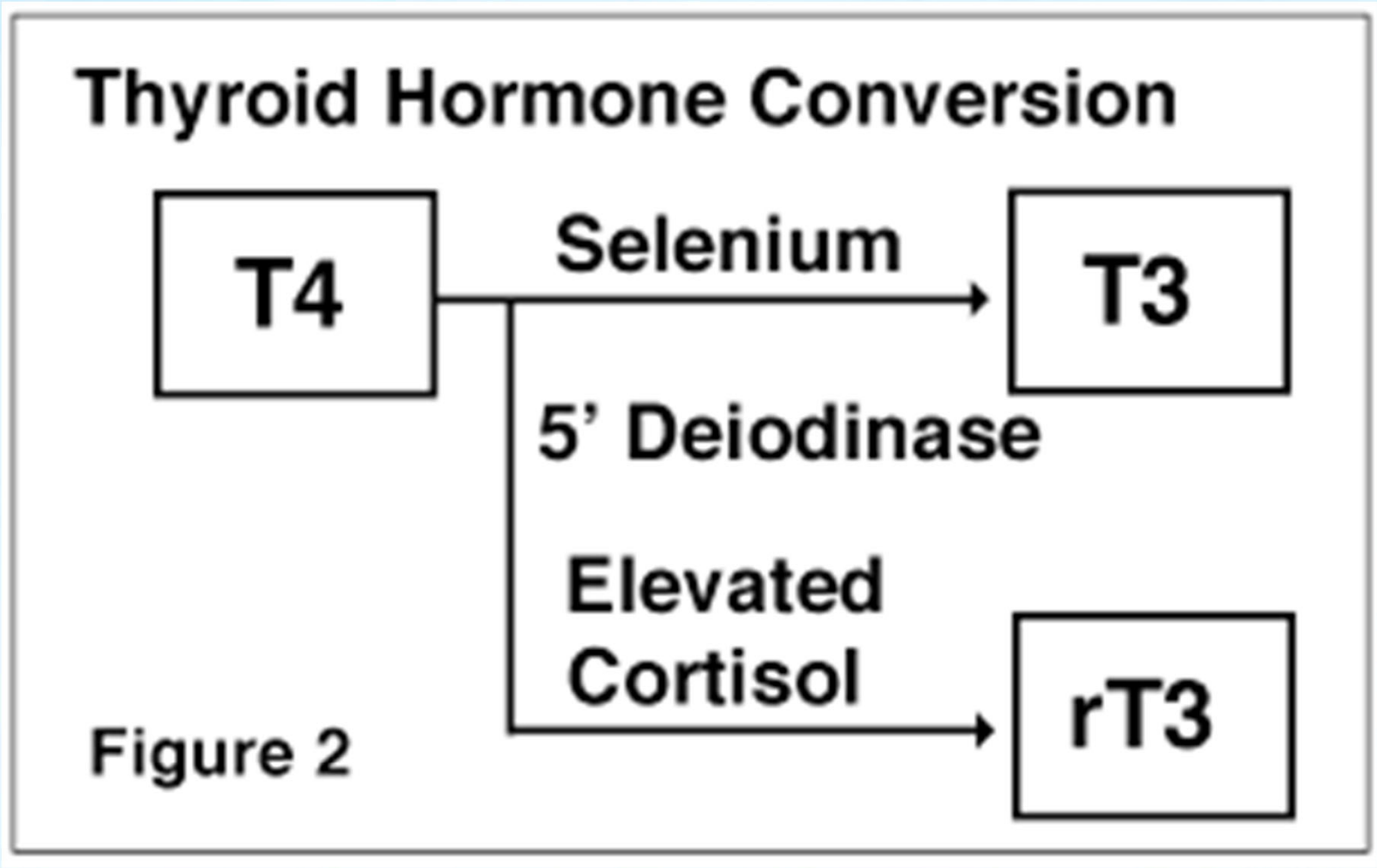
- 2013 randomized clinical study (n=390 elderly pts)
- 158 control, 92 cognitive impaired and 59 dementia
- Measured serum cortisol
- **RESULTS:** A positive correlation between elevated cortisol and dementia

Lara VP, et al. High cortisol levels are associated with cognitive impairment no-dementia (CIND) and dementia. Clin Chim Acta. 2013;423:18-22.

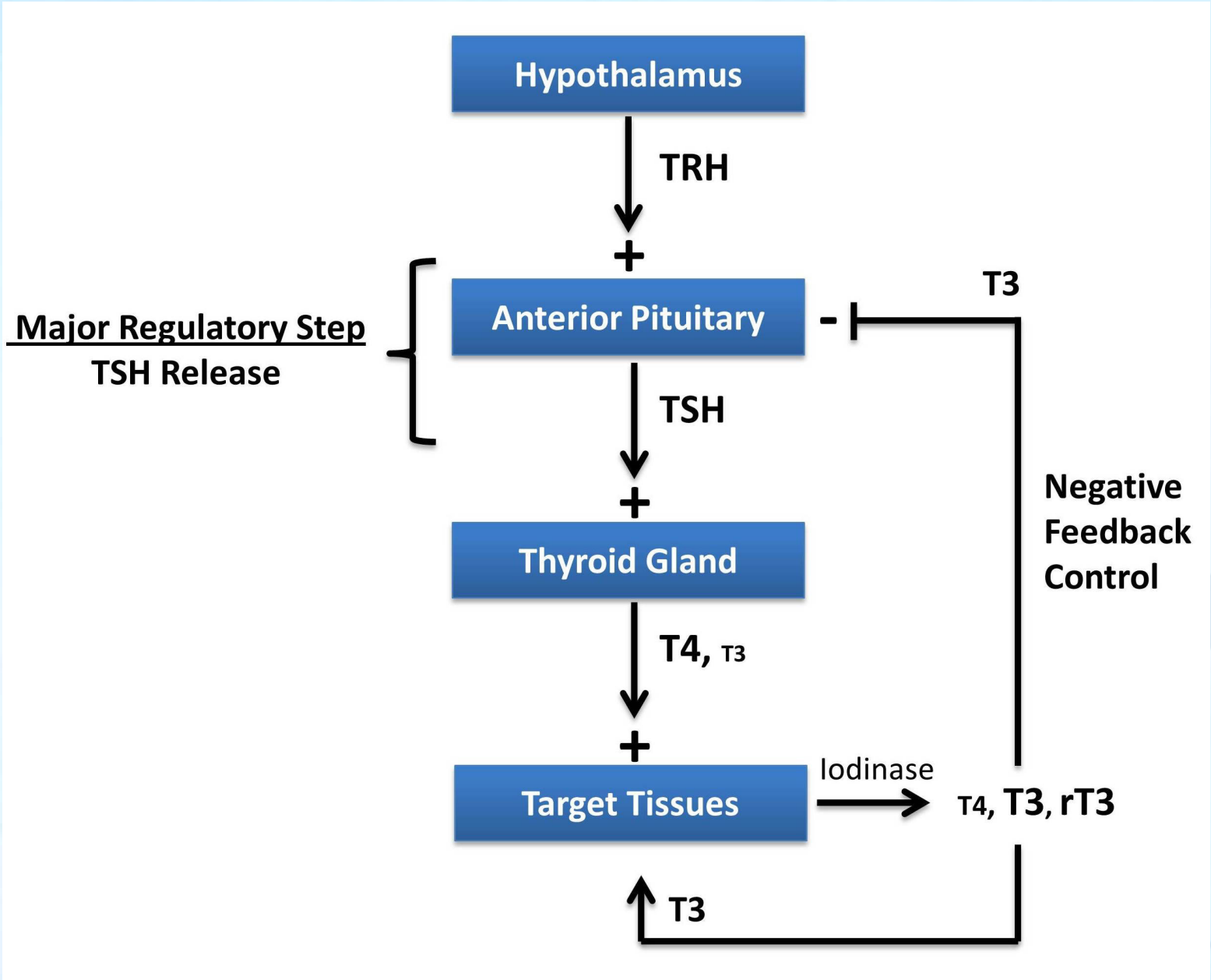
Cortisol and Thyroid Function



- Adrenal and thyroid function closely linked
- Both under control of hypothalamus and tropic hormones
- Thyroid competes with adrenals for tyrosine
- When tyrosine used to produce cortisol under stress not enough tyrosine left to make thyroid hormones



- rT3 Binds to T3 receptors
- Blocks T3 from binding


Hypothalamus
TRH
+
Major Regulatory Step
TSH Release
Anterior Pituitary
T3
-
TSH
+
Thyroid Gland
Negative
Feedback
Control
T4, T3
+
Target Tissues
Iodinase
T4, T3, rT3
T3

Stress and Thyroid Antibodies

- Reduced glucocorticoid activity is associated with an increased prevalence of ThAbs positivity in older ambulatory subjects.

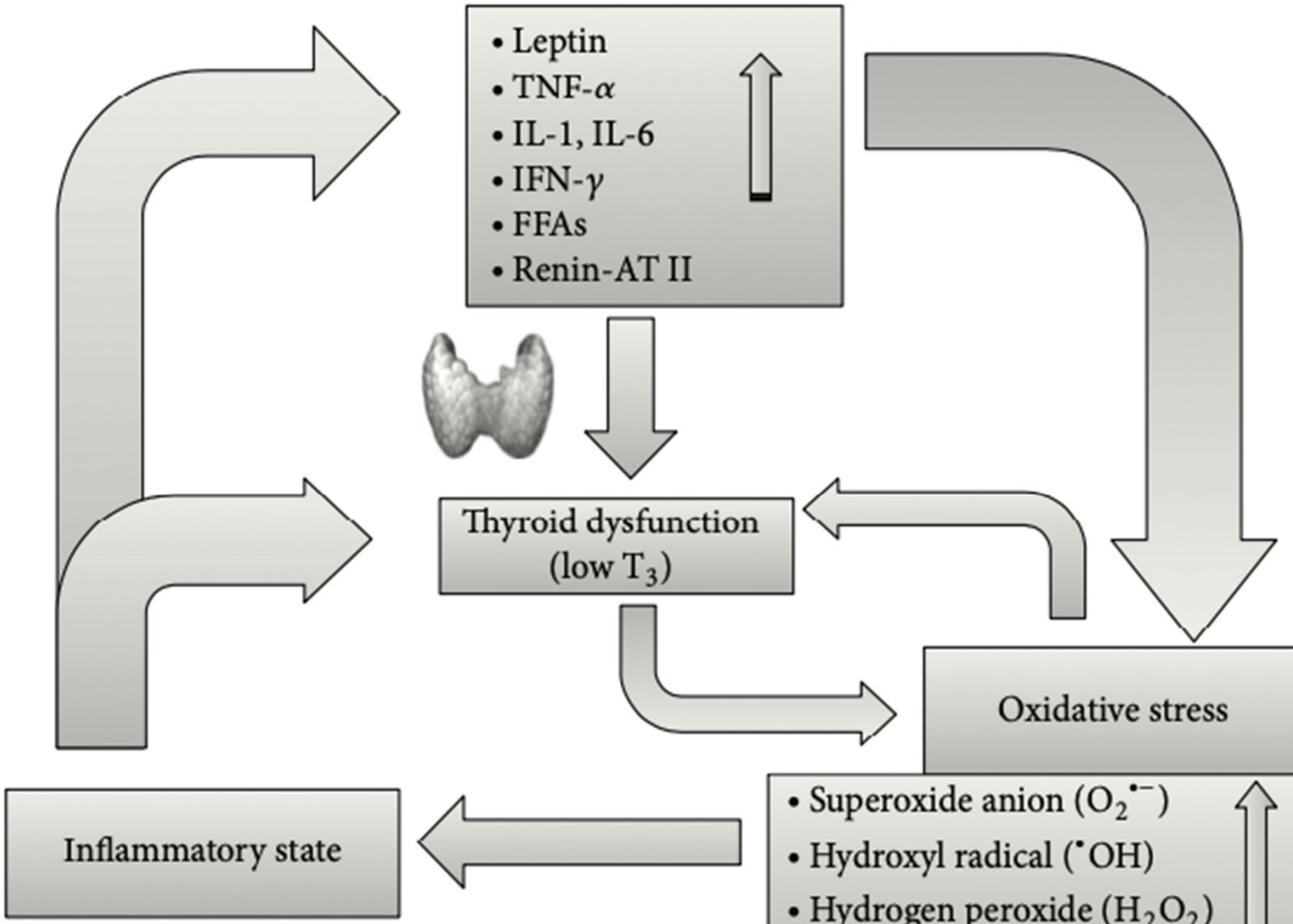
  Terzidis K, et al. Eur J Endocrinol. 2010;162(2):307-13

- HPA axis (neuro-endocrine) imbalances caused by stress-mediated activation

- Involved in autoimmune thyroid diseases (AITD)

  Klecha AJ, et al. Neuroimmunomodulation. 2008;15(1):68-75

ative Stress, flammation d Thyroid sfunction



i A, et al. Thyroid hormones, oxidative stress and mmation. Mediator Inflamm. 2016; 6757154.

Symptoms of Hypothyroidism
% of cases

- Weakness 99
- Dry skin 97
- Coarse skin 97
- Lethargy 91
- Slow speech 91
- Edema of eyelids. 90
- Cold hands and feet 89
- Decreased sweating 89
- Cold Skin 83
- Memory Impairment 66
- Constipation 61
- Weight gain 59
- Loss of hair 57
- Pallor of lips 57
- Dyspnea 55
- Peripheral edema 55
- Hoarseness or aphonia 55
- Anorexia 45

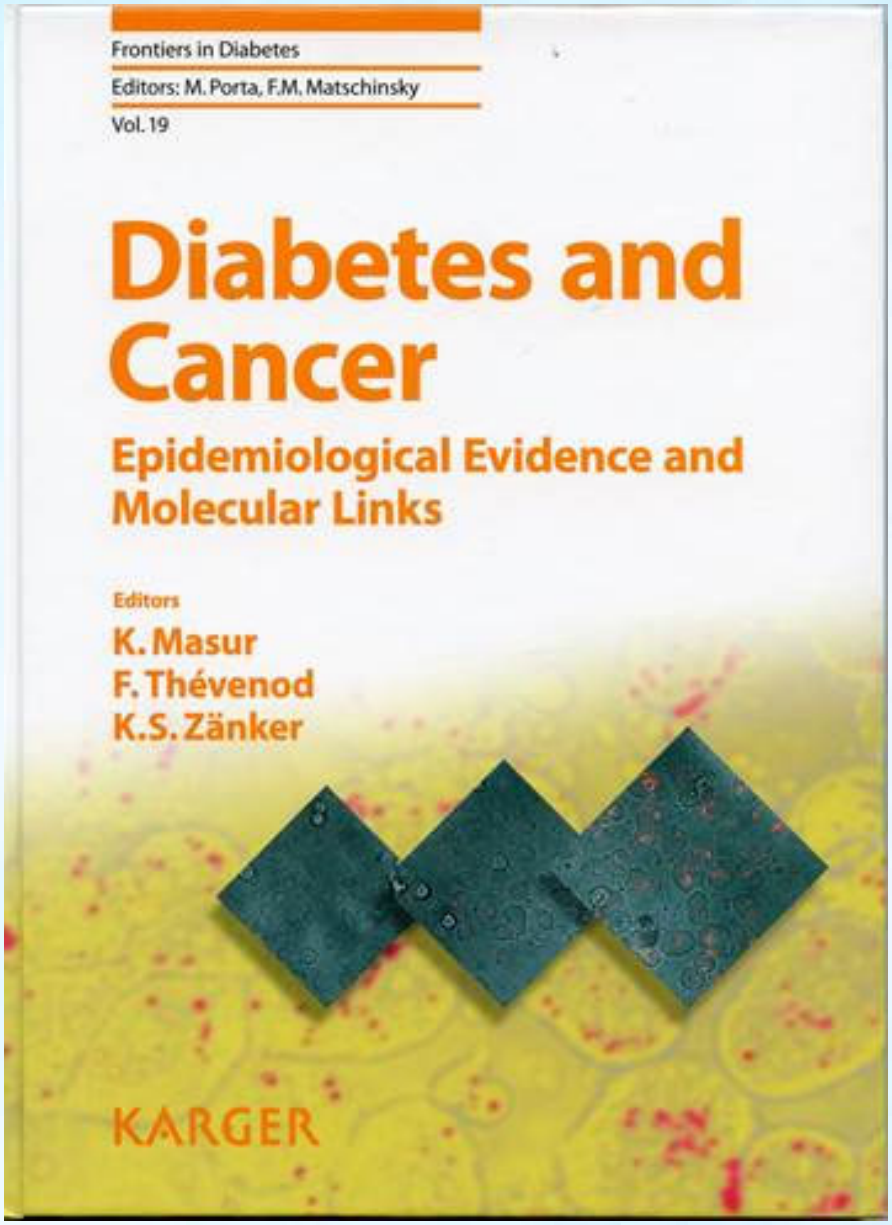
**BMJ* 1997;314:1175 (19 April)

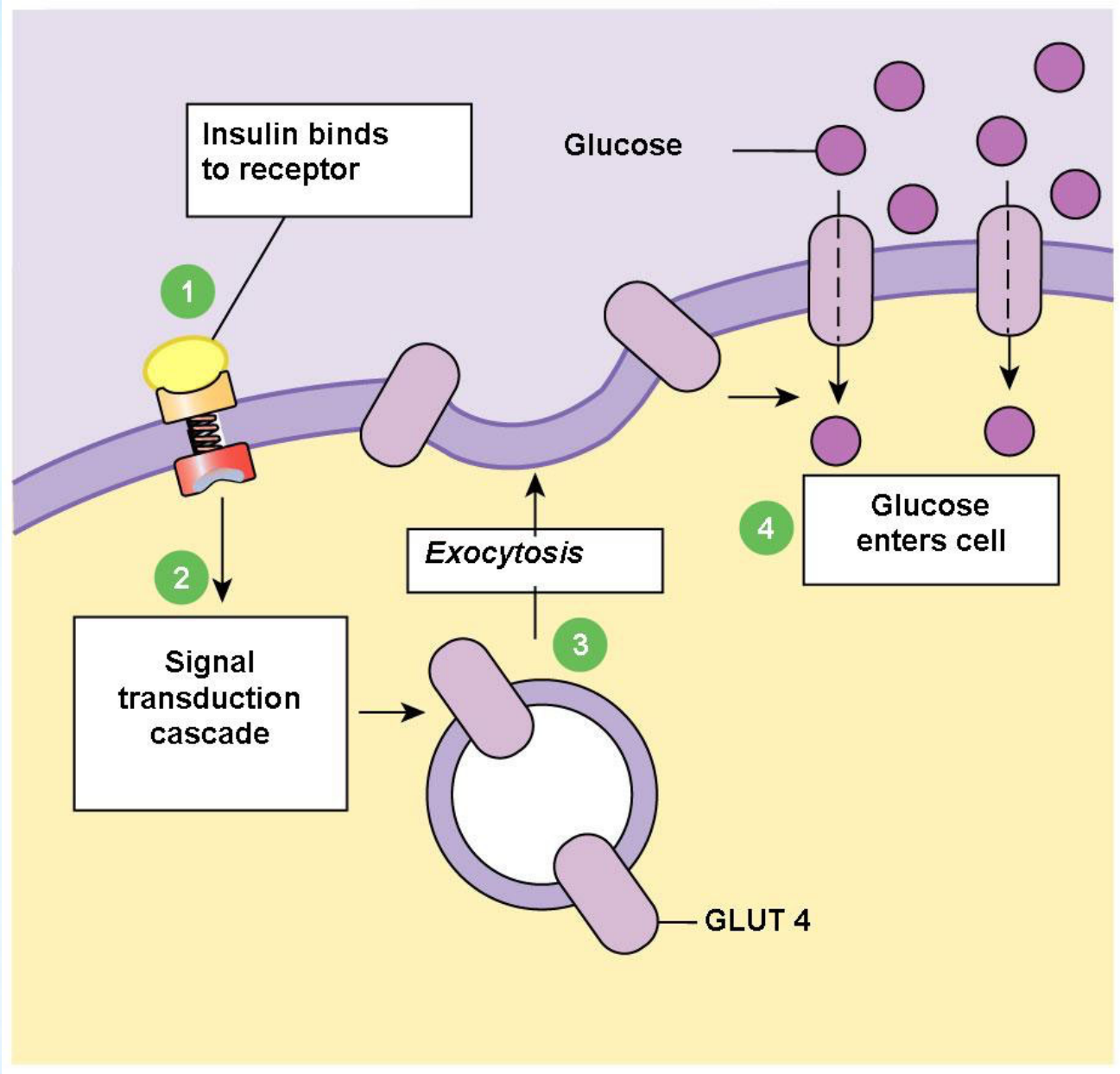
Metabolic Effects of Suboptimal Thyroid Function

Glucose tolerance

- Rate of glucose absorbed from GI tract and cellular uptake
- Insulin signaling/receptor problems
- Reduces target cell insulin binding/number of insulin receptor expressed
- Decreases metabolism fats and increases serum lipids & availability of cardioprotective essential fatty acids
- Decreases Inadequate T3 lowers oxygen consumption, contributes to lipids peroxidation and free radical damage

(J Clin Endocrin Metal, 82 (10) Oct. 1997)


Frontiers in Diabetes
Editors: M. Porta, F.M. Matschinsky
Vol. 19
Diabetes and Cancer
Epidemiological Evidence and Molecular Links
Editors
K. Masur
F. Thévenod
K.S. Zänker
KARGER


Insulin binds to receptor
Glucose
1
2
Signal transduction cascade
Exocytosis
3
4
Glucose enters cell
GLUT 4

TYPE 2 DIABETES

DIABETES STATS

25.8 million

More than 8 percent of the U.S. population has been diagnosed with diabetes.

79 million

Approximately 35 percent of adults, 20 and older, have prediabetes — most have not been diagnosed.

71,382

The number of deaths directly attributed to diabetes annually in the United States. Diabetes also contributes to another 231,404 deaths per year.

2050

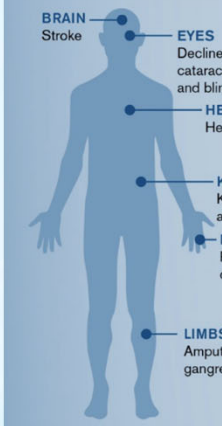
The year by which 1 in 3 Americans will have diabetes.

Types of Diabetes

- **5%** Type 1 diabetes
- **1-5%** Other types of diabetes
- **90-95%** Type 2 diabetes

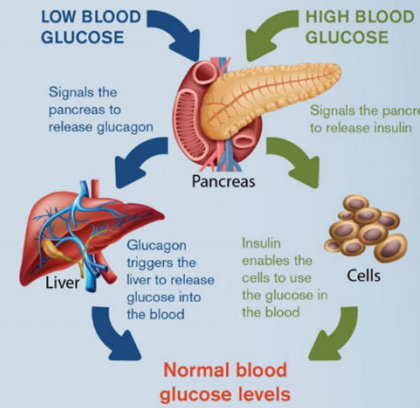
Source: American Diabetes Association

PARTS OF THE BODY COMMONLY AFFECTED BY TYPE 2 DIABETES

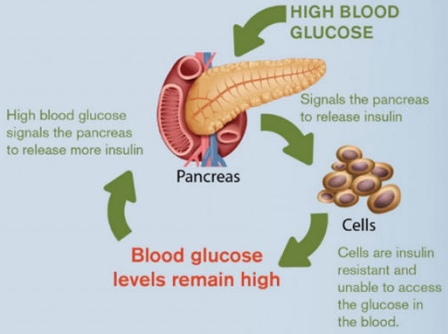


- **BRAIN** Stroke
- **EYES** Decline in vision, cataracts, glaucoma and blindness
- **HEART** Heart attack
- **KIDNEYS** Kidney failure, dialysis and kidney transplant
- **NERVES** Peripheral nerve damage, neuropathy
- **LIMBS** Amputation and gangrene

HOW THE BODY REGULATES BLOOD GLUCOSE



HOW THE BODY ATTEMPTS TO REGULATE HIGH BLOOD GLUCOSE IN TYPE 2 DIABETES



KNOW YOUR NUMBERS

Target Blood Glucose (mg/dl)

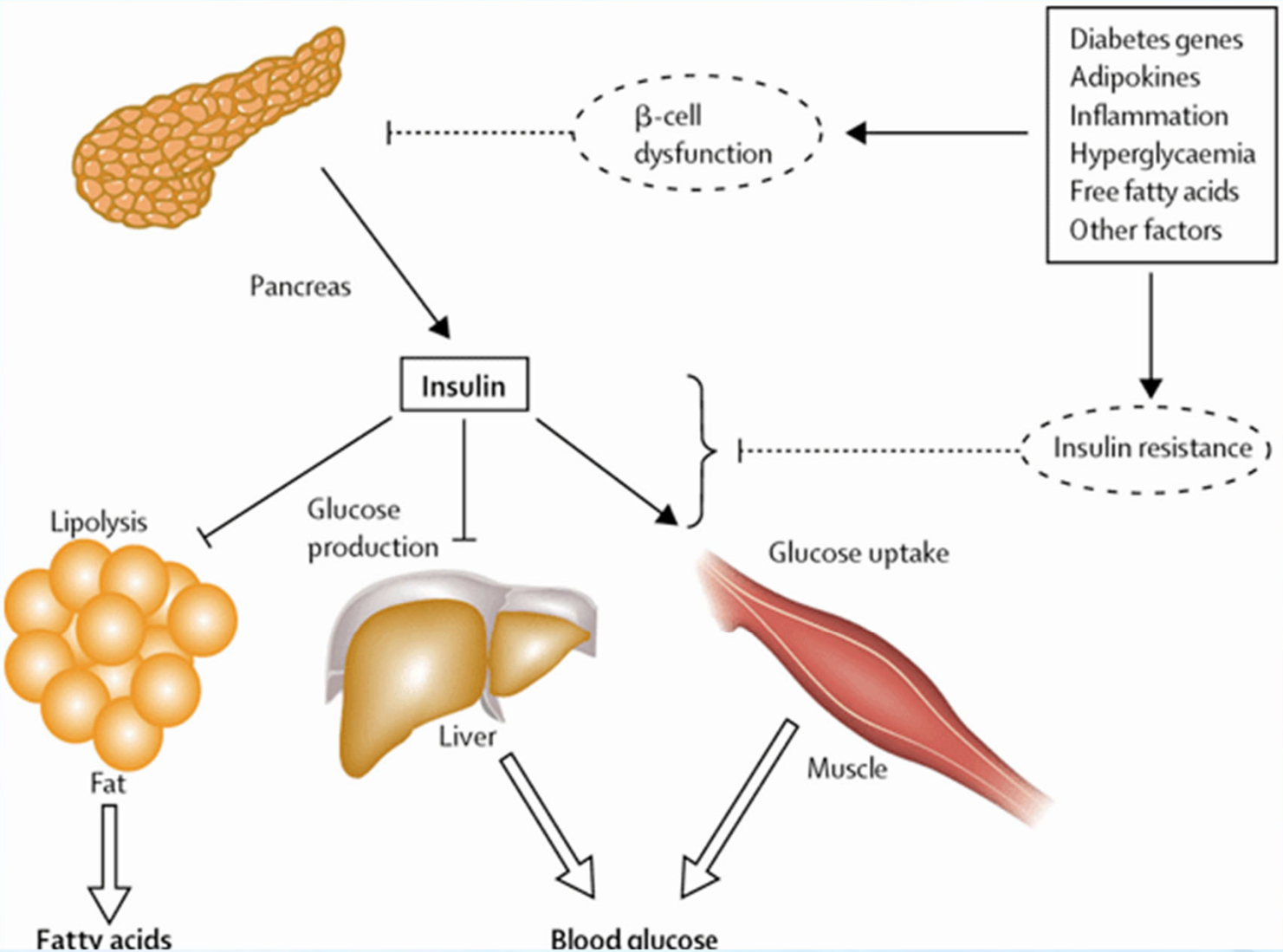
Fasting	Nonfasting (~2 hrs after a meal)
70-120	<180

Hemaglobin A1c (%)

Normal	Prediabetes	Diabetes
<5.7	5.8-6.5	>6.5

Source: National Institute of Diabetes and Digestive and Kidney Diseases

Actions of Insulin



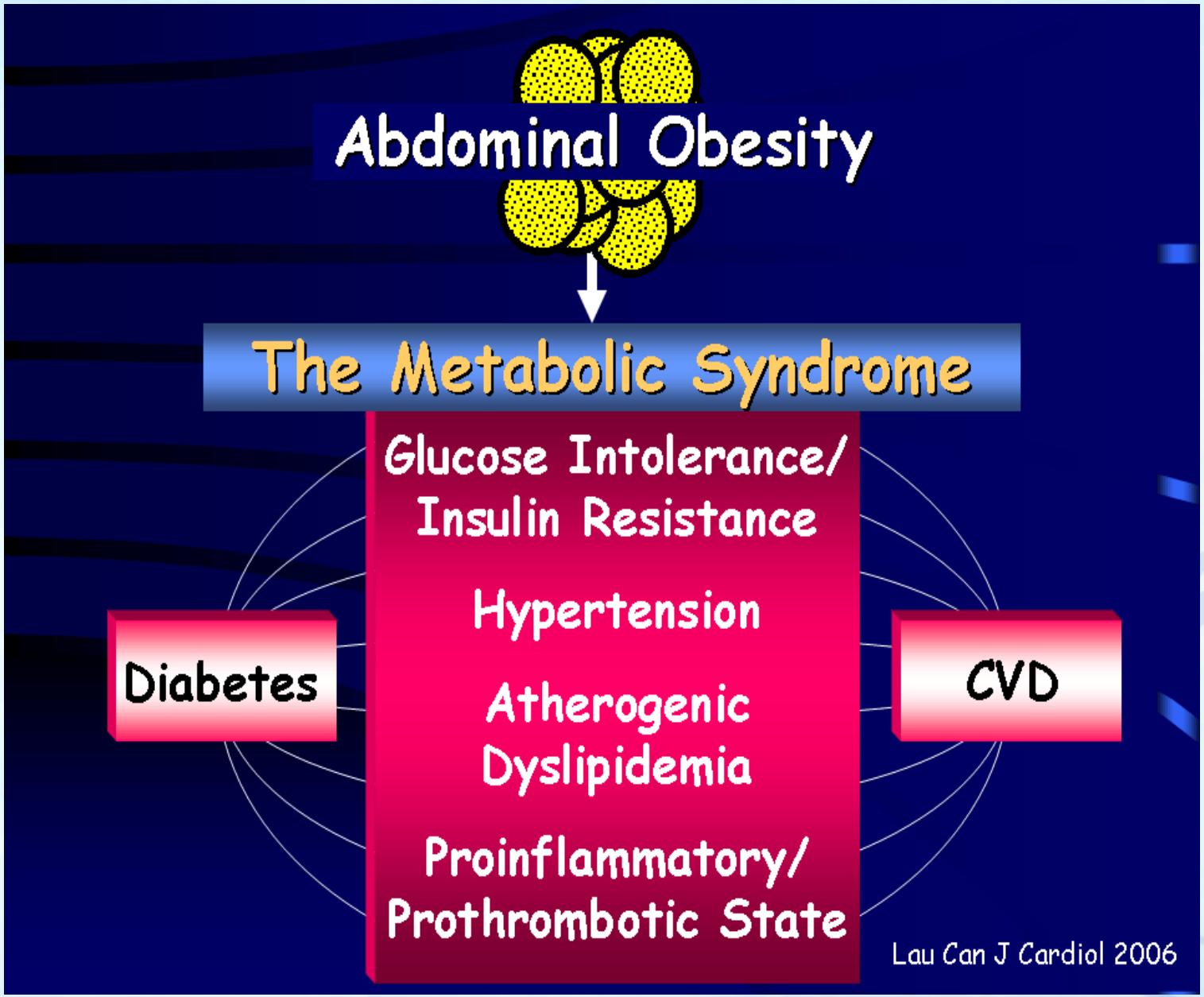
Visceral Fat: The Engine in the Belly

- ↑ Risk of insulin resistance
- ↑ Estrogen
- ↑ Aromatase
- ↑ Androgens
- ↑ PCOS (women)
- ↑ Angiotensinogen
- ↓ Growth hormone

Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev. 2000;21:697–738.

- ↑ TNF alpha
- ↑ Oxidative stress
- ↓ Glutathione
- ↑ Glycation
- ↑ Isoprostanes
- ↑ Interleukins, IL-6
- ↑ Risk non-alcoholic fatty liver

Matsuzawa Y. Establishment of a concept of visceral fat syndrome and discovery of adiponectin. Proc Jpn Acad Ser B Phys Biol Sci. 2010;86(2):131-41.


Abdominal Obesity
The Metabolic Syndrome
Glucose Intolerance/
Insulin Resistance
Hypertension
Atherogenic
Dyslipidemia
Proinflammatory/
Prothrombotic State
Diabetes
CVD
Lau Can J Cardiol 2006

Inflammation/Oxidative Stress in Obesity

- 93 women with BMI > 28
- Android vs. gynoid obesity
- Sharply elevated isoprostanes associated with WHR and BMI
- Weight reduction resulted in mean decline of isoprostanes:
  - 476 pg/mg creatinine baseline: - 166 pg/mg creatinine decline
- 10% reduction in body weight associated with 50% reduction in thromboxane synthesis

- ***Android obesity is associated with persistent inflammation and lipid peroxidation***

Davi G, et al. JAMA 2002 Oct 23-30;288(1

Oral Glucose Load, Inflammation and Oxidative Stress

- 21 patients with type 2 diabetes
- 75 g oral glucose load
- Isoprostanes measured and baseline and 90 min.
- Mean isoprostane elevation of 34%
  - Baseline = 0.241 ng/L
  - 90 minute = 0.326 ng/L
- Hyperglycemia induces free radical damage
- Post-prandial hyperglycemia may be associated with acute oxidative stress and may be independent predictor of cardiovascular mortality in type 2 diabetes

Sampson MJ, et al. Diabetes Care 2002 Mar;25(3):537-41.

Inflammation as a Cause of IR

- Excessive production of inflammatory compounds in the body can cause IR
- Inflammatory substances damage and/or inactivate insulin receptors.
- Contributes to breakdown of one or more factors needed to complete the process of glucose transport

Shoelson SE, et al. Inflammation from insulin resistance. J Clin Invest. 2006;116(7):1793-1801.

...and IR is a Cause of Inflammation

- IR leads to ↑ inflammatory markers
- Including ferritin, uric acid, white cell counts, fibrinogen, CRP and IL-6

Chen J, et al. Association Between Inflammation and Insulin Resistance in U.S. Nondiabetic Adults Results from the Third National Health and Nutrition Examination Survey, *Diabetes Care* 2004 (27):2960-2965.

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Every point over 84 fasting glucose represented a 6% increased risk of becoming diabetic

By blood level 90 vascular and kidney damage has already begun.

Nichols, Gregory, A, Hillier, Teresa A, Brown, Jonathan:Normal Fating Plasma Glucose and Risk of Type 2 Diabetes Diagnosis:The American Journal of Medicine Vol 121, Issue 6 Pages 519-524 (June2008)

Study Conclusion

- The strong independent association between the level of normal fasting plasma glucose and the incidence of diabetes after controlling for other risk factors suggests that diabetes risk increases as fasting plasma glucose levels increase, even within the currently accepted normal range.

Glucose Infusion and Inflammation

- 15 IGT subjects and 20 controls
- Received 3 consecutive glucose pulses (.33 g/kg) separated by 2-hour intervals
- IGT subjects had higher baseline TNFα and IL-6 levels than controls
- IGT subjects experienced significant increase in cytokines following glucose pulse
- Concomitant glutathione infusion negated rise in cytokines
- "Hyperglycemia increases circulating cytokine concentrations by an oxidative mechanism, and its effect is more pronounced in IGT."

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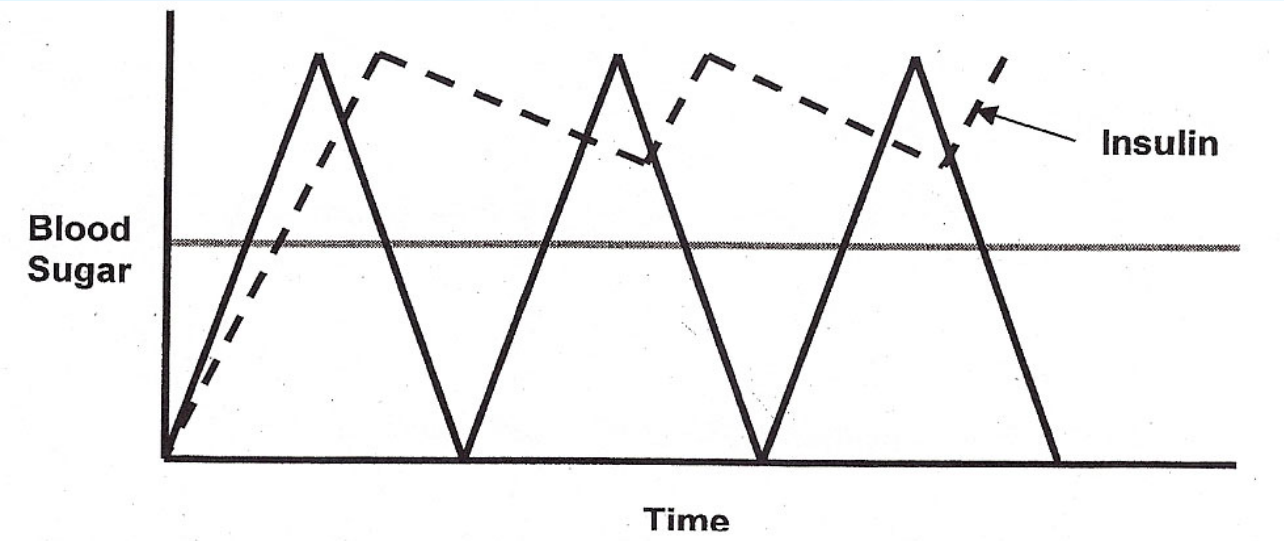
Does the Increase in Inflammatory Markers Increase the Risk to Diabetes?

- 27,628 women free from diabetes and cardiovascular disease (Women's Health Study)
- 188 women developed diabetes over 4-year follow-up
- CRP and IL-6 strongly associated with development of diabetes
- "Elevated levels of CRP and IL-6 predict the development of type 2 DM. These data support a possible role for inflammation in diabetogenesis."

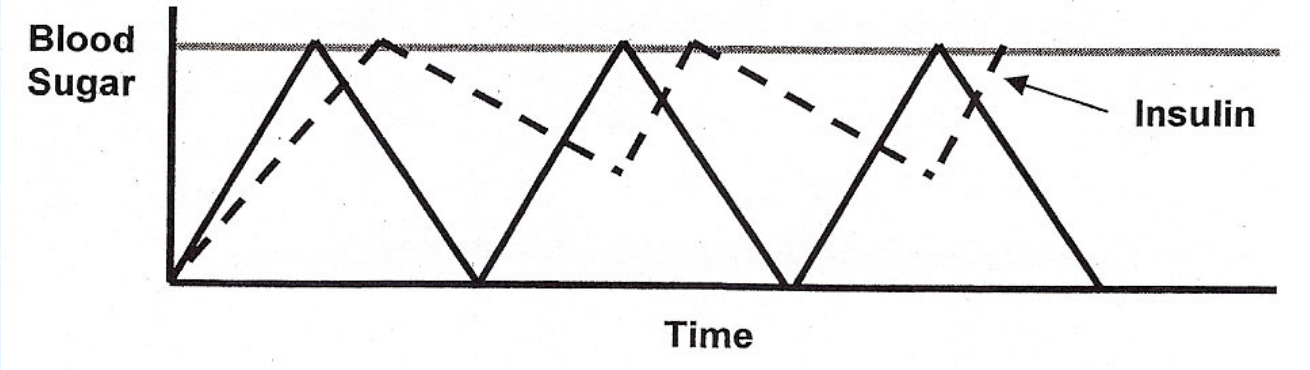
Pradhan AD, et al. JAMA 2001 Jul 18;286(3):327-34.

Blood Sugar & Insulin in High/Low Glycemic Meals

High

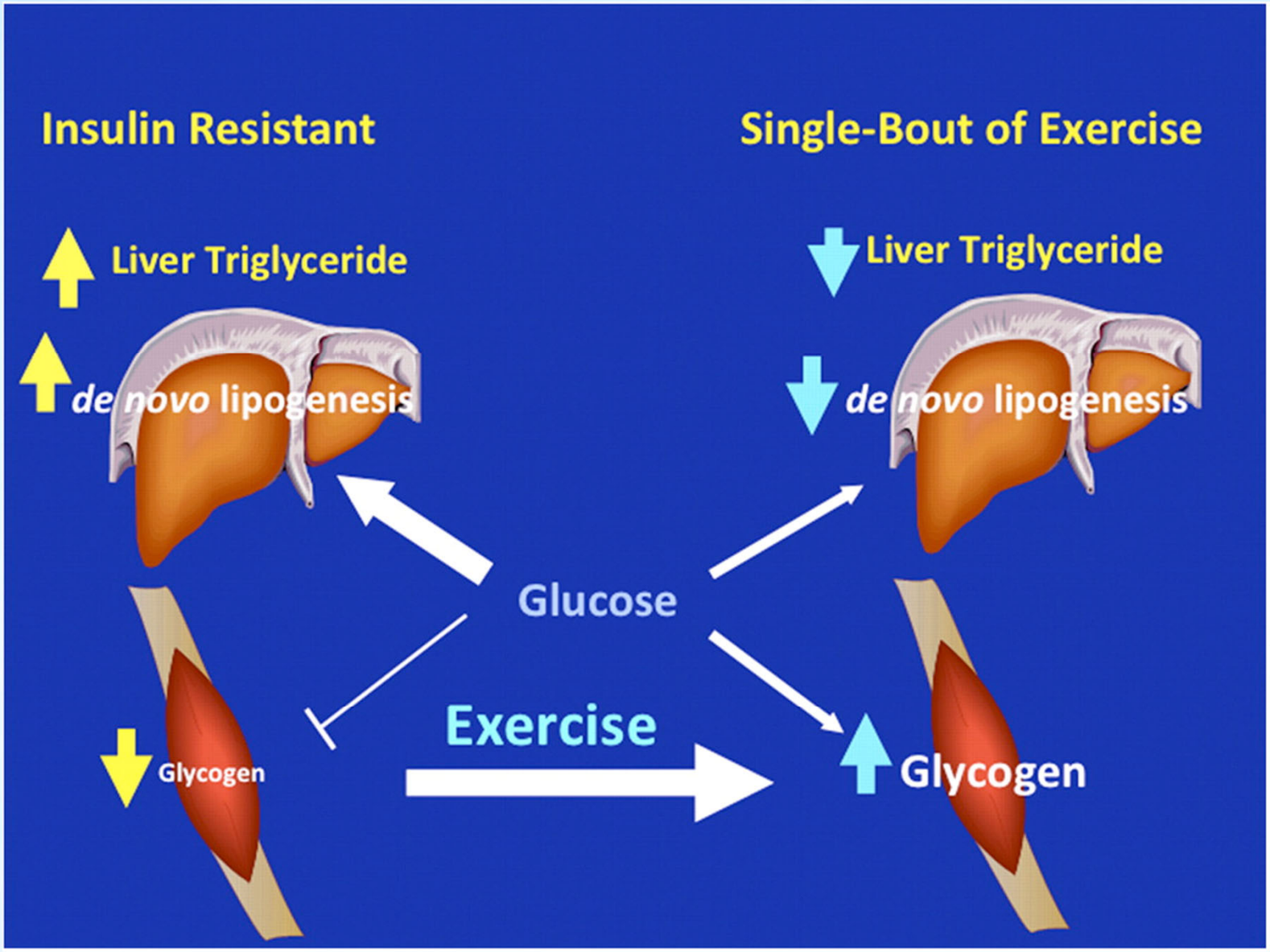


Low



Most beneficial and clinically relevant effect of exercise is the improvement in insulin sensitivity in skeletal muscle

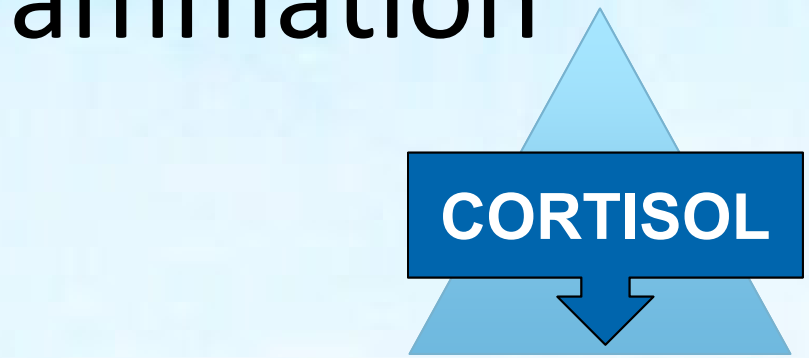
Lira VA, et al. PGC-1 alpha regulation by exercise training and its influences on muscle function and insulin sensitivity. Am J Physiol Endocrinol Metab. 2010;299(2):E145-E161.


Insulin Resistant
Single-Bout of Exercise
Liver Triglyceride
de novo lipogenesis
Liver Triglyceride
de novo lipogenesis
Glucose
Exercise
Glycogen
Glycogen

Important labs to Assess T1 Impact on Metabolic Signaling

- CBC, CMP
- CORTISOL 8am serum 18-25mcg/dL trending hi, > 25 hi
- Blood Pressure >120/80
- pH(salivary and urinary) < 6.8
- Sodium 140 ideal
- RBC Mag 5.8
- Potassium >4.5
- Serum Cortisol 10-15
- Salivary 4-point Cortisol or 5 point urinary
- SIgA varies but should be 3rd quartile
- DHEA 105-700 at least 300
- IGF-1
- Blood Glucose/Insulin/HbA1c/ Insulin
- Resting Pulse <70
- Thyroid panel – T3F, T4F, TSH, TyrAb, TPO, rT3

Inflammation



Tyrosine

I.R./DM	Thyroid	Gut/Immune
CRP↑ Adipose↑ Adiponectin↑	T4 ≠ T3 HypoThyroid	Inflam➔AutoImm Macrophages-Cytokines Hashimoto's Food allergies Viral load

TNF-a
IL-6

CV Disease

Cardiovascular disease is NOT simply a cholesterol issue

MC TRIAD 1 LAB REPORTING Example

HEALTH & VITALITY ASSESSMENT REPORT

abolic Code®

PRACTICE

Date: 8/19/2019
Metabolic Code Enterprise
Practitioner: Andrew Heyman

Lab Results

	NORMAL RANGE	MY LAB VALUES	MY PREVIOUS LAB VALUES	MY CURRENT LAB VALUES
				ALERT LOW / LOW NORMAL / OPTIMAL NORMAL / HIGH NORMAL / ALERT HIGH
Adrenal				T1 LAB VALUES
Cortisol (serum)	5.5-19.8	12.7		
DHEA-S serum	45-276	103		
pH (salivary)	5.0-8.0			
Sodium	133-145	142		
Thyroid				T1 LAB VALUES
T3 Free	2.0-4.4	3.4		
T4 Free	0.93-1.7	1.06		
T3 Total	80-200	108		
T4 Total	4.5-11.7	5.9		
Reverse T3	8-24	11		
Thyroid Antibodies	<30	< 10		
Thyroid Peroxidase	<34	< 10		
TSH	0.27-4.2	2.88		

HEALTH & VITALITY ASSESSMENT REPORT

Metabolic Code®

PRACTICE

Date: 8/19/2019
Metabolic Code Enterprise
Practitioner: Andrew Heyman

Lab Results

	NORMAL RANGE	MY LAB VALUES	MY PREVIOUS LAB VALUES	MY CURRENT LAB VALUES
				ALERT LOW / LOW NORMAL / OPTIMAL NORMAL / HIGH NORMAL
Pancreas				T1 L
BMI	18-35	26.62		
Adiponectin	>35	77		
Ferritin	13-150	98		
Glucose (fasting)	65-99	108		
Hemoglobin A1c	<5.6	5.8		
HDL	>49	71		
Insulin	3-9	9		
Leptin	< 43	51		
Potassium	3.5-5.3	4.5		
RBC Magnesium	4.2-6.8	6.3		

Supplement Support for TRIAD 1

- Supplements that target TRIAD 1 Adrenal imbalances:
  - Improve Hypothalamic/Pituitary/Adrenal (HPA) axis
  - Cortisol balance
  - Tuning the adaptive stress response
  - Target neurotransmitters involved in stress responses – dopamine, serotonin
  - Provide vitamins/minerals necessary for proper stress response

ADPT-CNS

- Helps body adapt to stresses, including physical/ otional/mental
- Improves cortisol levels and adrenal support
- HPA axis support
- Helps improve energy and stamina
- Used in stress and cortisol imbalances with or without anxiety

Adpt-CNS

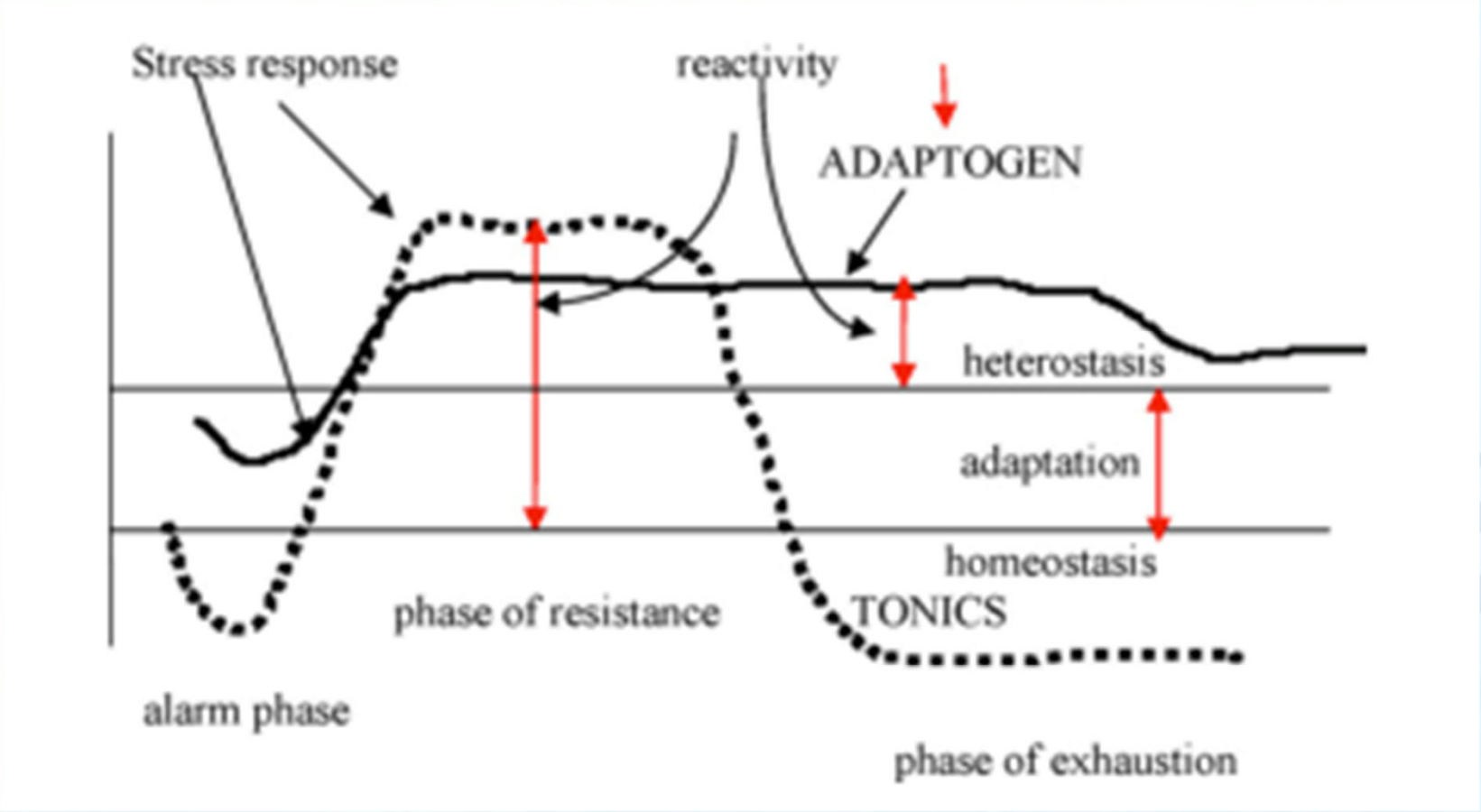
- Dosage: 2 capsules in the am, 1 capsule in the afternoon daily
- 3 capsules contain (daily dose):
  - Rhodiola (*Rhodiola rosea*) root 525 mg
    Std. to 5% rosavins
  - Cordyceps (*Cordyceps sinensis*) mycelia 1,000 mg
    4:1 extract
  - Thai ginseng (*Kaempferia parviflora*) root 100 mg
    std. to 4% 5,7 dimethoxyflavones
  - Schisandra (*Schisandra chinensis*) berry 225 mg
    std. to 9% schisandrins

Rhodiola (*Rhodiola rosea*) root

- "Second generation" plant adaptogen
- Used to support stress and stress response
- Helps balance cortisol and support adrenals
- Decreases anxiety
- Supports improved mental and physical performance

itsky A, Kerwin L, Feusner JD. A Pilot Study of Rhodiola rosea (Rhodax((R))) for Generalized Anxiety Disorder (GAD). J Altern Complement Med. 2008;14(2):175-80.
mtseva Y, et al. Rhodiola rosea in subjects with prolonged or chronic fatigue symptoms: results of an open-label clniacl trial. Complement Med Res. 2017;24(1):46-52.

Stress Response and Effects of Adaptogens



Adaptped from: Pannosian et al. Pharmacology of Schisandra chinensis Bail.: an overview of Russian research and uses in medicine. J Ethnopharmacol.
2008;118(2):183-212.

Rhodiola - Selected Clinical Studies

- 2011 systematic review of clinical studies on Rhodiola
  - 11 randomized, placebo-controlled clinical studies reviewed
  - Conclusion: Rhodiola has beneficial effects on:
    - Physical Performance
    - Mental Performance
    - Mood Stabilization
- 2017 open-label, multicenter, single-arm trial (n=118, male/female)
  - Patients presented with adrenal “burnout”
  - 400 mg daily single dose of rhodiola standardized extract for 12 weeks
  - Results: Significant improvement in symptoms after 1 week of therapy continued improvement

erry R, Ernst E. The effectiveness and efficacy of Rhodiola rosea L.: a systematic review of randomized clinical trials. Phytomedicine. 235-44.

t al. Multicenter, open-label, exploratory clinical triad with Rhodiola rosea extract in patients suffering from burnout symptoms. iat Dis Treat. 2017;22:889-898.

Cordyceps (*Cordyceps sinensis*)

- Caterpillar mycelium
- Used for adaptogenic and immune support
- Decreases oxidative stress
- Supports kidney function
  - Reported to protect against aminoglycoside and cyclosporine toxicity

al., CordyMax Cs-4: A Scientific Product Review. Pharmanex Phytoscience Review Series, 1997.
C., Chou, C. J., Lin, L. C., Tsai, W. J., and Kuo, Y. C. Immunomodulatory functions of extracts from the Chinese medicinal fungus Cordyceps cicadae.
armacol. 2002;83(1-2):79-85.

Cordyceps (Cordyceps sinensis)

- Improves cellular oxygenation; improves VO2
- Increased sexual vitality in both men and women
- Direct action on sexual center of brain/ HPA axis

J, et al., CordyMax Cs-4: A Scientific Product Review. Pharmanex Phytoscience Review Series, 1997.

ng, S. C., Chou, C. J., Lin, L. C., Tsai, W. J., and Kuo, Y. C. Immunomodulatory functions of extracts from the Chinese medicinal fungus Cordyceps cicadae. thnopharmacol. 2002;83(1-2):79-85.

2014 Cordyceps Study - Cochrane Database Review

- Cordyceps in the treatment of chronic kidney disease (CKD)
- 22 clinical studies, 1746 patients
- RESULTS: Cordyceps as an adjuvant to conventional CKD therapy
  - Decreased serum creatinine
  - Increased creatinine clearance
  - Reduced proteinuria
  - Alleviated CKD-associated complications including:
    - Increased hemoglobin
    - Increased albumin

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Cordyceps Clinical Study

- 2010 clinical trial (n=20 healthy adults aged 50-75 yrs)
- Cordyceps Cs-4 333mg tid or placebo x 12 wks
- Metabolic threshold (above which lactate accumulates) increased by 10.5%
- Ventilatory threshold (above which unbuffered H(+) stimulates ventilation) increased by 8.5%

Chen et al. Effect of Cs-4 (Cordyceps sinensis) on exercise performance in healthy older subjects: a double-blind, placebo controlled trial. J Altern Complement Med. 16(5):585-90.

Thai Ginseng (Kaempferia parviflora) root

- aka Black Ginger - in the ginger family
- Contains high level of antioxidant polymethoxyflavones specifically 5,7 dimethoxyflavones
- Improves mitochondrial biogenesis – increased energy
- Improves stress reduction
  - 2018 clinical study n= 80
  - Raw *Kaempferia parviflora* root 360mg/day for 14 days
  - Improved HR variability
  - Decreased stress based on Hamilton Anxiety Rating Scale (HAM-A)

Eungpinichpong W, et a
of Kaempferia parviflora
physical and psycholog
stresses in adults. Int J
GEOMATE. 2018;15(5)

Thai Ginseng root

- Improves weight management
  - SIRT1 and PPAR gamma regulating
  - Increases whole-body energy expenditure (EE)
  - Improves brown adipose tissue (BAT) production
- PDE5 inhibitor - improves nitric oxide utilization
- Traditionally used in erectile dysfunction
- Reported to improve athletic performance based on stress response and cardiorespiratory performance

Kim M, Awa R, Kuwahara awada T. 2014. parviflora extract increases umption through activation ce. Food Sci Nutr 2: 634–

, et al. Effect of parviflora extract on ss of soccer players: A double blind placebo

Thai Ginseng

- 2015 clinical study (n=22 healthy males)
- Single 100mg dose of standardized thai ginseng
- Improved while body energy expenditure (EE) significantly at 60 minutes vs. placebo
- A 2010 clinical study (n=19 and n=16) reported no benefit of acute ingestion of Thai ginseng on sprint and endurance exercise performance

Matsushita et al. Kaempferia parviflora Extract Increases Whole-Body Energy Expenditure in Humans: Roles of Brown Adipose Tissue. J Nutr Sci Vitaminol. 2015;61:79-83

Wasuntarawat C, et el. No effect of acute ingestion of Thai ginseng (Kaempferia parviflora) on sprint and endurance exercise Performance in humans. J Sports Sci. 2010;8(11):1243-50.

Thai Ginseng

- 2010 clinical study (n=19 and n=16 healthy males)

- Single doses of standardized thai ginseng
- N=19 patients exercised to exhaustion

- Improved while body energy expenditure (EE) significantly at 60 minutes vs. placebo

Matsushita et al. Kaempferia parviflora Extract Increases Whole-Body Energy Expenditure in Humans: Roles of Brown Adipose Tissue. J Nutr Sci Vitaminol. 2015;61:79-83

Schisandra *(Schisandra chinensis)*

Berry

- Traditional Chinese Medicine Herbal adaptogen
- Adaptogen
- Hepatoprotective – supports Phase I metabolism
- Neuroprotective
- Immune supportive
- Most published clinical research from Russia and China

RD, Mao YW, Leu SJ, et al. The immune-regulatory effects of Schisandra chinensis and its constituents on human monocytic leukemia cells. Molecules. 2011;16(6):4836-49.

ee SB, et al. Induction of the phase II detoxification enzyme NQO1 in hepatocarcinoma cells by lignans from the fruit of chisandra chinensis through nuclear accumulation of Nrf2. Planta Med. 2009 Oct;75(12):1314-8.

Schisandra

- Listed as a drug in the National Pharmacopoeia of the USSR and in th

State Register of Drugs :

  - Antifatigue

  - The 8th ed. Of Russian Medicinal Drugs – Manual on Pharmacoth Doctors, states “Schisandra has a stimulating effect on the CNS, t cardiovascular system and the respiratory system. In the event o exhaustion, it increases the capacity for work…”

Schisandra Clinical Studies

- Numerous Russian clinical studies (pre-2000) report:
  - Increased capacity for physical work
  - Improved endurance; decreased fatigue
  - Improved mental performance
  - Decreased stress
  - Improved accuracy of movement

Pannosian et al. Pharmacology of Schisandra chinensis Bail.: an overview of Russian research and uses in medicine. J Ethnopharmacol. 2008;118(2)

Adpt-CNS Cautions

- Adpt-CNS is used for stress and adrenal support
- Adpt-CNS is used for elevated TRIAD 1 points in the MC
- Thai ginseng is a PDE5 inhibitor, so using a pharmaceutical PDE5 conc not recommended
- Thai ginseng also is reported to alter CYP34A hepatic metabolism
  - A case study reported lowered acetaminophen levels

  when taking Thai ginseng concurrently

  - Another case study reported increased midazolam t1/2 and increase

et al. In vivo effect of
rviflora extract on
tics of acetaminophen.
xicol. 2019;1-7.[Epub
.

Adrenal Complex

- Formulated to support stress and adrenal function
  - Improved cortisol regulation
  - Improved cellular energy production and utilization
  - Improved energy, stamina and performance

- Used in low cortisol labs and no anxiety can be pulsed to match c

rhythm

Adrenal Complex

Supplement Facts

Serving Size: 2 Capsules Servings per Container: 60

	Amount Per Serving	% Daily Value*
Vitamin C (Ascorbic Acid)	175 mg	290%
Calcium (Calcium Citrate)	87 mg	10%
Vitamin A (Palmitate)	3333 IU	70%
Thiamin (Vitamin B1)	8.5 mg	570%
Riboflavin (Vitamin B2)	6.7 mg	400%
Niacinamide (Vitamin B3)	50 mg	250%
Pyridoxine (Vitamin B6)	16.7 mg	840%
Pantothenic Acid (Vitamin B5)	8.4 mg	90%
Zinc (Aspartate)	8.3 mg	60%
Adrenal Tissue	175 mg	**
Spleen Tissue	175 mg	**

* Percent Daily Values are based on a 2000 calorie diet.
** Daily Value not established.

- Dose = 1 capsules AM, 1 capsule NOON daily

QuiCalm

Used for:

- Stress, anxiety and to promote relaxation
- Supports stress-related eating issues

Helps balances cortisol levels

Decreases stress and anxiety

Improve neurochemical balance to reduce stress-related food cravings

1 cap three times per day

Relora®

- Relora
  - Proprietary blend of Chinese herbs *Magnolia* and *Phellodendron* (bark)
  - Used for Stress and Stress-related appetite control
  - Anti-anxiety and anti-stress properties rival benzodiazepines, yet non-sedating and no “hangover” effect
  - Improves cortisol balance

Kishi E, Hattori N, Okada M, Maruyama Y. The anxiolytic effect of two oriental herbal drugs in Japan attributed to honokiol from magnolia bark. J Pharm Pharmacol. :1425-9.

Y, Kuribara H, Morita M, Yuzurihara M, Weintraub ST. Identification of magnolol and honokiol as anxiolytic agents in extracts of saiboku-to, an oriental herbal medicine. 1998;61:135-8.

l. Effect of a proprietary Magnolia and Phellodendron extract on stress levels in healthy women: a pilot, double-blind,placebo-controlled clinical trial. Nutr J. 2008;7(1):11.

Relora Study

- Double blind-placebo controlled clinical study (n=26)
  - Overweight, otherwise healthy premenopausal females
  - 250mg tid x 6 weeks
  - Significantly reduced transitory anxiety and stress-related eating

Kishi E, Hattori N, Okada M, Maruyama Y. The anxiolytic effect of two oriental herbal drugs in Japan attributed to honokiol from magnolia bark. J Pharm Pharmacol.):1425-9.
Y, Kuribara H, Morita M, Yuzurihara M, Weintraub ST. Identification of magnolol and honokiol as anxiolytic agents in extracts of saiboku-to, an oriental herbal medicine. 1998;61:135-8.
l. Effect of a proprietary Magnolia and Phellodendron extract on stress levels in healthy women: a pilot, double-blind,placebo-controlled clinical trial. Nutr J. 2008;7(1):11.

Relora Clinical Studies

- 2013 clinical study (n=56) published in Journal of International Society of Sports Nutrition
- 250mg bid x 4 weeks
- Improved salivary cortisol
- Improved mood
- Improved overall well-being and decreased stress

Talbott et al. Effect of Magnolia officinalis and Phellodendon amurense (Relora) on cortisol and psychological mood state in moderately stressed subjects. J Int Soc Sports Nutr. 2013;10(1):37.

Holy Basil (*Ocimum sanctum*)

- In Hindi known as Tulsi
- Used for 3000 years – The “Elixir of Life” in Ayurveda
- Adaptogenic
- Immunomodulatory – increase NK and T-helper cells in humans
- Cognitive/mood improvement in humans

shidi N, et alhe Clinical Efficacy and Safety of Tulsi in Humans: A Systematic Review of the Literature. Evid Based Comlement Alternati Med. 2017;2017:9217567.

rgava KP, Singh N. Anti-stress activity of *Ocimum sanctum* Linn. *Indian* Journal of Medical Research. 1981;73:443–451.

Holy Basil (*Ocimum sanctum*)

- Antioxidant
- Antifatigue
- Hepato- and Radio Protective
- Blood glucose effects – metabolic supportive

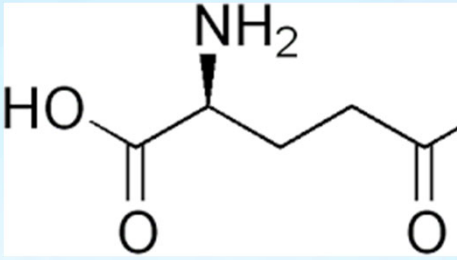
N, et alhe Clinical Efficacy and Safety of Tulsi in Humans: A Systematic Review of the Literature. Evid Based Comlement Alternati Med. 2017;2017:9217567.

Holy Basil Clinical Study - Stress

- 2011 Study (n=79, 6 weeks) to evaluate a proprietary holy basil extract in stress
- 1,200mg daily x 6 weeks
- Results = 39% improvement in stress symptoms vs. placebo
- No adverse events/ well tolerated

na RC, et al. Efficacy of an Extract of *Ocimum tenuiflorum* (OciBest) in the Management of General Stress: A Double-Blind, Placebo-Controlled Study. Evid Based
olement Alternat Med. 2012;2012:894509.

L-Theanine



- Amino acid found in green tea (*Camellia sinensis*)
- Acts antagonistically against the stimulatory effects of caffeine in the tea on the nervous system
- Glutamate antagonist
  - Indirectly increases GABA (gamma-amino-butyric acid)
  - balances the excitability that can sometimes lead to restlessness, insomnia, and other disruptive conditions
- Antianxiety

L-Theanine

- Cognitive and mood support
- Increases levels of dopamine
- Dampens Phenylethylamine (PEA)
- Increases alpha waves
- Good for sleep if daytime drowsiness a problem

L-Theanine Studies

Sharma E. L-theanine: an astounding sui generis integrant in tea. Food Chem. 2018;242:601-10.

Saaed M, et al. Green tea (camellia sinensis) and L-theanine: medicinal values an beneficial applications in humans – A comprehensive review. Biomed Pharmacother. 2017;95:1260-1275.

Kobayashi et al. Effects of L-theanine on the release of -brain waves in human volunteers. Nippon Noegik Kaishi 72(2):153-57.

Hidese S, et al. Effects of chronic l-theanine administration in patients with major depressive disorder: an open-label study. Acta Neuropsychiatr. 2017;29(2):72-79.

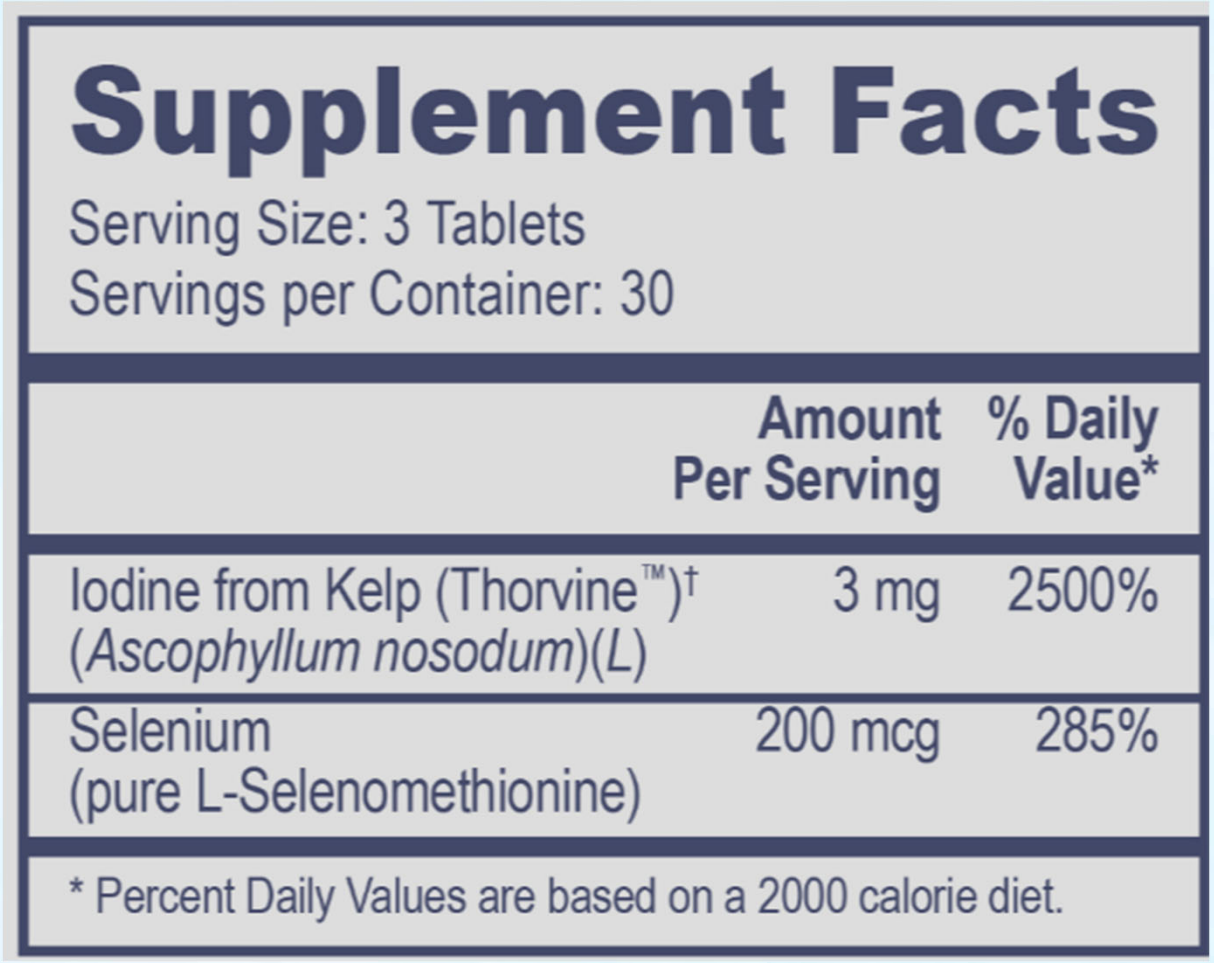
Supplement Support for TRIAD 1 Thyroid Support

- Supplements that target TRIAD 1 Thyroid imbalances:
  - Improve Thyroid hormone balance
  - Support energy production and mitochondrial health
  - Supports thermogenesis and fat burning
  - Provide nutrients essential for thyroid health
  - Improves body composition

Selenometh Iodine – T1 Thyroid

- Features targeted nutrients that support thyroid function
- Supports production and release of thyroid hormones
- Leads to improved energy
- Supports improved body composition and metabolism
- Studies suggest 1 in 10 people in US suffer from some form of thyroid disorder = metabolic imbalance

Selenometh Iodine



Supplement Facts

Serving Size: 3 Tablets
Servings per Container: 30

	Amount Per Serving	% Daily Value*
Iodine from Kelp (Thorvine™)† (*Ascophyllum nosodum*)(*L*)	3 mg	2500%
Selenium (pure L-Selenomethionine)	200 mcg	285%

* Percent Daily Values are based on a 2000 calorie diet.

Dose = 1 tab TID

OR ThyroComplex

- Supports thyroid hormone synthesis and release

- Formulary use for low thyroid hormone labs

- Dose – 2 AM , 1 early afternoon

Supplement Fa

Serving Size: 1 Capsule
Servings per Container: 90

	Amount Per Serving
Calcium	160 mg
Iodine	1500 mcg
Thyroid Tissue	55 mg
Adrenal Tissue	25 mg
Pituitary Tissue	25 mg
Thymus Tissue	5 mg
Spleen Tissue	5 mg

* Percent Daily Values are based on a 2000 calorie diet.
** Daily Value not established.

Thyroid Support – Antibodies?

- **If no antibodies:**
- Selenometh Iodine – 1 tab TID
- Provides all nutrients needed to support thyroid hormone production
  - Iodine – kelp 3mg/3
  - Selenium- cofactor in T4/T3 conversion

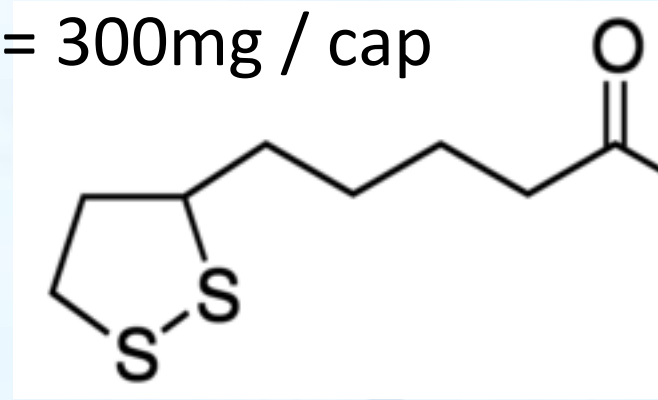
- **If high antibodies:**
- Low allergen diet
- Balance gut – Berberine/cat's claw, L-Glutamine, AAE powder, Aloe, probiotics, digestive enzymes
- Moducare - plant sterols balance immune cells
- Check for environmental exposures (heavy metals)
- Check stress hormones

Supplement Support for TRIAD 1: Pancreas Support

- Improve blood sugar levels
- Improve glucose regulation
- Improve insulin signaling to decrease insulin resistance
- Provide herbs and nutrients essential for blood glucose regulation

ALA Forte'

- Alpha lipoic acid, mixed racemic = 300mg / cap
- AKA thioctic acid
- Antioxidant
- Anti-metaflainflammatory
  - Decreases Th1 mediated inflammatory processes
- Cardio and Renal supportive

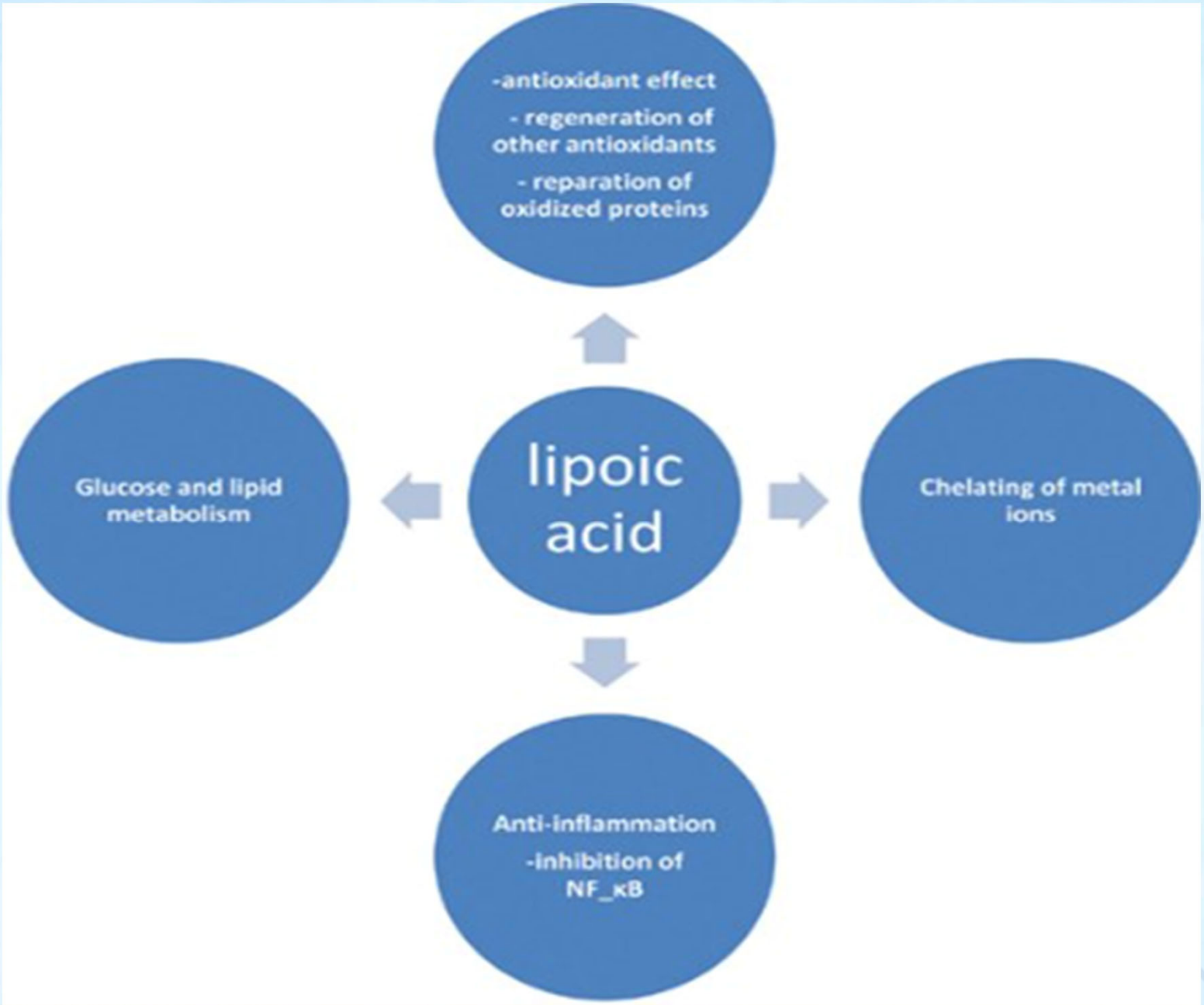


Zhang J, et al. Lipoic acid in the prevention of acute kidney injury. Nephron. 2016;134:133-140.
Merida S, et al. Free Radic Res. 47(8):593-601.

Alpha Lipoic Acid (ALA)

- Decreases diabetes complications – oxidative stress induced
- Reported to improve insulin sensitivity
- Improved glycemic control
- Reduced incidence/symptoms of neuropathies

Padmalayam I, et al. ipoic acid synthase (LASY): a novel role in inflammation, mitochondrial function, and insulin resistance. Diabetes. 2009 Mar;58(3):600-8.


-antioxidant effect
- regeneration of other antioxidants
- reparation of oxidized proteins
Glucose and lipid metabolism
lipoic acid
Chelating of metal ions
Anti-inflammation
-inhibition of NF_κB

ALA Mechanisms

- Naturally occurring lipoic acid = lipollysine
  - High levels in Spinach, Broccoli, tomatoes
  - ALA reduced to dihydrolipoic acid (DHLA) intracellularly
- Both ALA and DHLA act as a free radical scavenger of ROS and RNOS in vivo
- Mechanisms related to the phosphatidylinositol 3-kinase/Akt/Nrf2 pathway an the PI3-kinase/Akt pathways
  - Cell survival
  - Myocardial preconditioning
  - Myocardial contractility
  - Antiinflammation

Zhang J, et al. Lipoic acid in the prevention of acute kidney injury. Nephron. 2016;134:133-140.

ALA Mechanisms

- mprove glucose and ascorbate handling
- ncrease endothelial nitric oxide synthase activity
- Activate phase II detoxification via the transcription factor Nrf2
- Lower expression of matrix metalloproteinase-9 and vascular cell adhesion molecule-1 through repression of nuclear factor-κB (NF-κB)
- Metal chelation/detoxification

Biewenga GP, Haenen GR, Bast A: The pharmacology of the antioxidant lipoic acid Pharmacol 1997; 29: 315–331.

ALA Mechanisms

- Affects beta cell function
- ↑cAMP-activated protein kinase (AMPK)
- ↑ PGC-1 alpha, ↑ PPAR alpha
- Improves glucose utilization and mitochondrial biogenesis
- Studies report exercise and ALA therapy improves IRS-1 dependent insulin signaling

Henriksen EJ. Exercise training and the antioxidant alpha-lipoic acid in the treatment of insulin resistance and type 2 diabetes. Free Radic Biol Med. 2006 Jan 1;40(1):3-12. Review.

ALA Studies

- 2011, Double-blinded, randomized, placebo-controlled clinical trial
- N= 63 patients (ages 22-79) - **End Stage Renal Disease** undergoing maintenanc hemodialysis (HD)
- Supplemented w/ ALA 600mg or placebo. X 8 weeks
- RESULTS:
  - **CRP-hs significantly decreased – av. 18.7%**
- Authors conclude: ALA supplementation significantly reduced hsCRP levels, which is a risk factor for cardiovascular disease in HD patients.

Khabbazi T, et al. Effects of alpha lipoic acid supplementation in inflammation, oxidative stress and serum lipid profile levels in patients with end stage renal disease on hemodialysis. J Renal Nutr. 2011;

ALA

- 2018 meta analysis of 12 trials
- ALA effects on weight/body mass
- Up to 1,200 mg daily
- RESULTS:
  - Slight but significant decrease in weight and BMI
  - ALA treatment 1.27 kg greater increase in wt loss over placebo

Namazi N, et al. Alpha lipoic acid supplement in obesity treatment: a systematic review and meta analysis of clinical trials. Clin Nutr. 2018;37(2):419-428.

ALA Forte' Dosage

- 1 capsule (300mg) - 2 times daily
- TRIAD 1 and 4 support
- Higher dosages may be necessary depending on clinical presentation
  - Eg. 1,500mg daily for weight loss support

Gluco-Beta Stimulator Plus

- Composed of herbs and nutrients to support pancreas and blood glucose/insulin regulation
- Helps control:
  - Carbohydrate metabolism
  - Balance blood sugar
  - Improve insulin signaling
- Used for HIGH TRIAD 1 pancreas points
- FBS - > 90 (trending hi 90-99, hi > 99)

Gluco-Beta Stimulator Plus

=

AM, 2 caps

cg chromium
cotinate daily

Supplement Facts

Serving Size: 1 Capsule
Servings per Container: 120

	Amount Per Serving	% Daily Value
Biotin	2 mg	667%
Chromium (Polynicotinate)(GTF)	100 mcg	83%
Proprietary Blend	700 mg	
Gymnema Sylvestre (Herb)(P.E. 4:1)		*
Cinnamon Bark (10:1 Extract) (*Cinnamomum verum*)		
Mulberry Leaf (4:1 Extract) (*Morus Alba*)		
Alpha Lipoic Acid		
Fenugreek Seed (*Trigonella foenum-graecum*)(*L*)		
Banaba Leaf (10:1 Extract) (*Lagerstroemia speciosa*)		
Vanadyl Sulfate	3 mcg	

* Daily Value not established.

Gluco-Beta Stimulator Plus

Blood sugar regulating Botanicals – Proven Clinical Results:

- *Gymnema sylvestre* Powdered extract 4:1
- Cinnamon bark (*Cinnamomum verum*) 10:1
- Mulberry leaf 4:1
- Fenugreek seed (Trigonella foenum-graecum)
- Banaba leaf 10:1

Khan F, et al. Comprehensive Review on Phytochemicals, Pharmacological and Clinical Potentials of *Gymnema sylvestre.* Front Pharmacol. 2019;10:1223

Ranasinghe P, et al. Efficacy and safety of 'true' cinnamon (Cinnamomum zeylanicum) as a pharmaceutical agent in diabetes: a systematic review and meta-analysis. Diabet Med. 2012;29(12):1480-

Gluco-Beta Stimulator Plus

Pancreas and BS Supportive Nutrients:

- GTF Chromium polynicotinate 100mcg/cap - 400mcg/day
  - Depleted nutrient in pre-diabetes (IR), diabetes and obesity
  - Meta-analyses report chromium consistently improves HOMA-IR
- Alpha lipoic acid
  - Antioxidant
  - Improves insulin sensitivity
  - Also supports renal function
- Vanadyl sulfate 3mcg/cap 6mcg/day
- Biotin

Suksomboon N, et al. Systematic review and meta-analysis of the efficacy and safety of chromium supplementation in diabetes. J Clin Pharm Ther. 2014;39(3):292-306.
Smith DM, Pickering RM, Lewith GT. A systematic review of vanadium oral supplements for glycaemic control in type 2 diabetes mellitus. QJM. 2008;101(5):351-8.
Missaoui S, et al. Vanadyl sulfate treatment stimulated proliferation and regeneration of beta cells in pancreatic islets. J Diabetes Res. 2014;115512014/54022.
Singh U, et al. Alpha-lipoic acid supplementation and diabetes. Nutr Rev., 2008;66(11):646-57.

Additional Pancreas Support

- If additional pancreas support is needed then use **Glucogen Complex**
- Blood glucose / insulin support
- Contains GTF chromium polynicotinate 200 mcg/2 caps
- Other important nutrients for Pancreas support - B vits, Mg, Se, Iodine, Glandular tissues
- 2 – 4 caps daily (200 – 400 mcg chromium daily) in addition to GlucoBeta-Stimulator Plus (@400mcg/day)

Supplement Fa

Serving Size: 2 Capsules Servings per Container: 60

	Amount Per Serving	% Daily Value*		Am Per Se
Vitamin C (Ascorbic Acid)	200 mg	330%	Selenium Oxide (Dioxide)	5
Thiamine (HCl)	35 mg	2330%	Manganese (Ascorbate)	
Riboflavin	35 mg	2060%	Chromium (GTF)	20
Niacin (Niacinamide)	350 mg	1750%	Pancreas Tissue	
Vitamin B6 (Pyrioxine HCl)	35 mg	1750%	Liver Tissue	
Vitamin B12 (Cyanocobalamin)	20 mcg	330%	Adrenal Tissue	
Biotin	100 mcg	30%	Thyroid Tissue	
Pantothenic Acid (Calcium Pantothenate)	100 mg	1000%	Alfalfa Herb Powder	
Iodine (Kelp)	40 mcg	25%	Peppermint Leaf	
Zinc (Ascorbate)	15 mg	100%		

* Percent Daily Values ar
2000 calorie diet.
** Daily Value not establis

True Chelate Magnesium

- Magnesium bisglycinate chelate 150mg elemental Mg^{++} per capsule
- Magnesium replenishment and improved metabolic signaling
- Used in those not needing full support of herbs/nutrients but still need glucose/insulin management
- 70% Americans deficient in magnesium
- Many
- Many drugs deplete magnesium – diuretics, PPIs, HRT/OCs, others

G, Roemmich
on ML, et al.
m deficiency
ted with
sistance in
ldren.
Care.
):1175-81.

True Chelate Magnesium

ported in studies:

- Improves GLUT4 in skeletal muscle
- Improves glycogen synthesis
- Improves pancreatic beta-cell proliferation and regeneration

pports all TRIADS 1-5

ue Chelate Magnesium = 150mg elemental magnesium
sglycinate chelate / capsule

se 2 caps AM , 2-3 caps PM

750 mg elemental Mg^{++})

to 800mg daily

True Chelate Magnesium 2

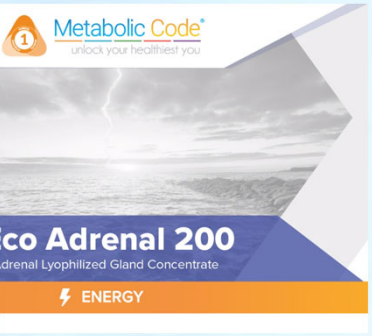
Supplement Facts

Serving Size: 1 Capsule
Servings per Container: 120

	Amount Per Serving	% Daily Value
Buffered Magnesium Glycinate Chelate (provides 150mg of Elemental Magnesium)	833 mg	35%

* Percent Daily Values are based on a 2000 calorie diet.

Other TRIAD 1 Supplements



- Eco Adrenal
  - New Zealand Adrenal tissue concentrate Extract 200mg/cap
  - For low cortisol levels with NO ANXIETY
  - Helps support adrenals and cortisol output
  - 1-2 caps AM, 1 cap noon or early afternoon
- Adrenal Cortex 250mg pure cortex for low cortisol and anxious
- Eco Thyroid 125 mg
  - New Zealand thyroid glandular tissue 125mg/cap
  - For Low thyroid hormone (Low T3, T4, Elevated TSH)
  - Subclinical hypothyroidism and overt hypothyroidism WITH LA checked

Other TRIAD 1 Supplements

- Metabolic Enhancer
- Helps support T1 Imbalances
- Dosage :

2 caps AM, 1 cap noon

Supplement Fa

Serving Size: 1 Capsule Servings per Container: 90

	Amount Per Serving
Biotin	1 mg
Pantothenic Acid (as Calcium Pantothenate)	100 mg
Iodine (Thorvine Organic Kelp™) (*Ascophyllum nodosum*)	50 mcg
Zinc (Aspartate Proteinate)	10 mg
Copper (Aspartate)	1 mg
Chromium (GTF Polynicotinate)	50 mcg
Vitamin C (Ascorbic Acid)	250 mg
L-Tyrosine	100 mg
Cinnamon (*Cinnamomium cassia*)	50 mg
Adrenal Medulla	50 mg
Thyroid	50 mg
Brain Tissue	50 mg
Hypothalamus	5 mg

AMLA-C

- Phyllanthus emblica fruit 500mg standardized to 50% vitam C/cap
- Ayurvedic antifungal/antibacterial botanical
- Dysbiosis corrective
- Also lipid supportive
- 1 cap BID before meals

Supplement Fact

Serving Size: 1 Capsule
Servings per Container: 90

	Amount Per Serving	% Da Val
Calcium (as phosphate)	60 mg	
Monolaurin	300 mg	
Inosine	7.5 mg	

* Percent Daily Values are based on a 2000 calorie die
** Daily Value not established.

Other Ingredients: Organic brown rice flour, Hypromellose and water (vegetarian capsule).

- Krishnaveni M, et al. Therapeutic potential of Phyllanthus emblia (amla): the Ayurvedic wonder. J Basic Clin Physiol Pharmacol. 2010;21(1):93-105

Thymus

- New Zealand Bovine Glandular - thymus
- Colds/flu support
- Extra Immune support
- 1 cap TID

Supplement Fac

Serving Size: 1 Capsule
Servings per Container: 90

	Amount Per Serving	%
Thymus Tissue	250 mg	

* Percent Daily Values are based on a 2000 calorie
** Daily Value not established

Other Ingredients: Gelatin and Water.

MISC. Metabolic Code Supplements

a dietary supplement take 1 Level Scoop,
. Mix in 10-12 oz. fruit juice, as a smoothie or

se Only.
lated product made from superior
controlled to ensure optimumpotency.

oy, yeast, dairy, gluten, artificial colors, flavors,

GLUTEN FREE
istered trademark of Taiyo International.
Seal. If Seal Is Broken, Do Not Use

ts have not been evaluated by the
Administration. This product is not
ose, treat, cure, or prevent any disease.

6 49818 19315 5

Metabolic Code®
unlock your healthiest you

ADPT Cell Signal

Reorder Code:
MCAAE

RESILIENCY

GUT - IMMUNE - BI

4.4 oz. (125 grams) I Dietary Supplement

SUPPLEMENT F
Serving Size 1 scoop (1.4g) • Servings p

Amount Per Serving	
Calories: 4	
Total Carbohydrates	0.2 g
Dietary Fiber	0.2 g
Soluble Fiber	0.2 g
Sugars	0.0 g
Avian Albumin Extract (A.A.E. - Norwegian source)	1000 mg
Aloe Vera Extract (*Aloe barbadensis*)(gel)(200:1)	200 mg
Sunfiber® Guar Fiber (partially hydrolyzed Guar gum) (*Cyamopsis Tetragonolobus*)	

* Percent Daily Values are based on a 2,000 c
† Daily Value not established.

Other Ingredients: Organic rice extract blend.

Metabolic Code
1271 Ida St. Cincinnati, OH 4520
MetabolicCode.com

Adpt-Cell Signal

- Immune supportive powder
- Stress support
- TRIADs 1, 2 and 3

- Contains per scoopful (1.4gm):
  - Avian Egg Albumin Extract (AAE), Norwegian source. 1gm
  - *Aloe barbadensis* gel extract 200:1, organic 200mg
  - Sunfiber® soluble guar gum fiber 200mg

Adpt-Cell Signal - AAE

- Avian Egg Albumin Extract (AAE)
- Powdered, fertilized, partially incubated eggs
- Clean Norwegian sources
- Reported to contain high levels of fibroblast growth fact (FGF)
  - FGF decreases as we age
  - FGF released locally upon tissue injury or tissue remodeling

Burgess WH, WH; Maciag, T. The heparin-binding (fibroblast) growth factor family of proteins. Annu Rev Biochem. 1989;**58**: 575–606.

Adpt-Cell Signal

- AEE contains FGF-2 – responsible for stem cells
- FGF required for full development of embryo
- When taken internally, signals body to maintain and repair damaged or a cells
- Helps body maintain homeostasis

Burgess WH, WH; Maciag, T. The heparin-binding (fibroblast) growth factor family of proteins. Annu Rev Biochem. 1989;**58**: 575–606.

Adpt-Cell Signal - AAE Benefits

- Stress support
  - Helps adapt to stress – HPA axis and direct action on adrenals
  - Improves 17-ketosteroid levels in adrenals
  - Actually decreases cortisol
  - Human study (n=28) reported Avian Egg Albumin
    - Reduced salivary cortisol by av. of 23.7% (27.3% women, 19.2% men)
    - Reduced HR
    - Decreases anxiety associated w/ chronic stress

Schult J, et al. Effects of powdered fertilized eggs on the stress response. Clin 2010;29(2):255-60.

AAE Stress Support – erceived State of Anxiety

Schult J, et al. Effects of owdered fertilized eggs n the stress response. Clin Nutr. 2010;29(2)(:255-60.

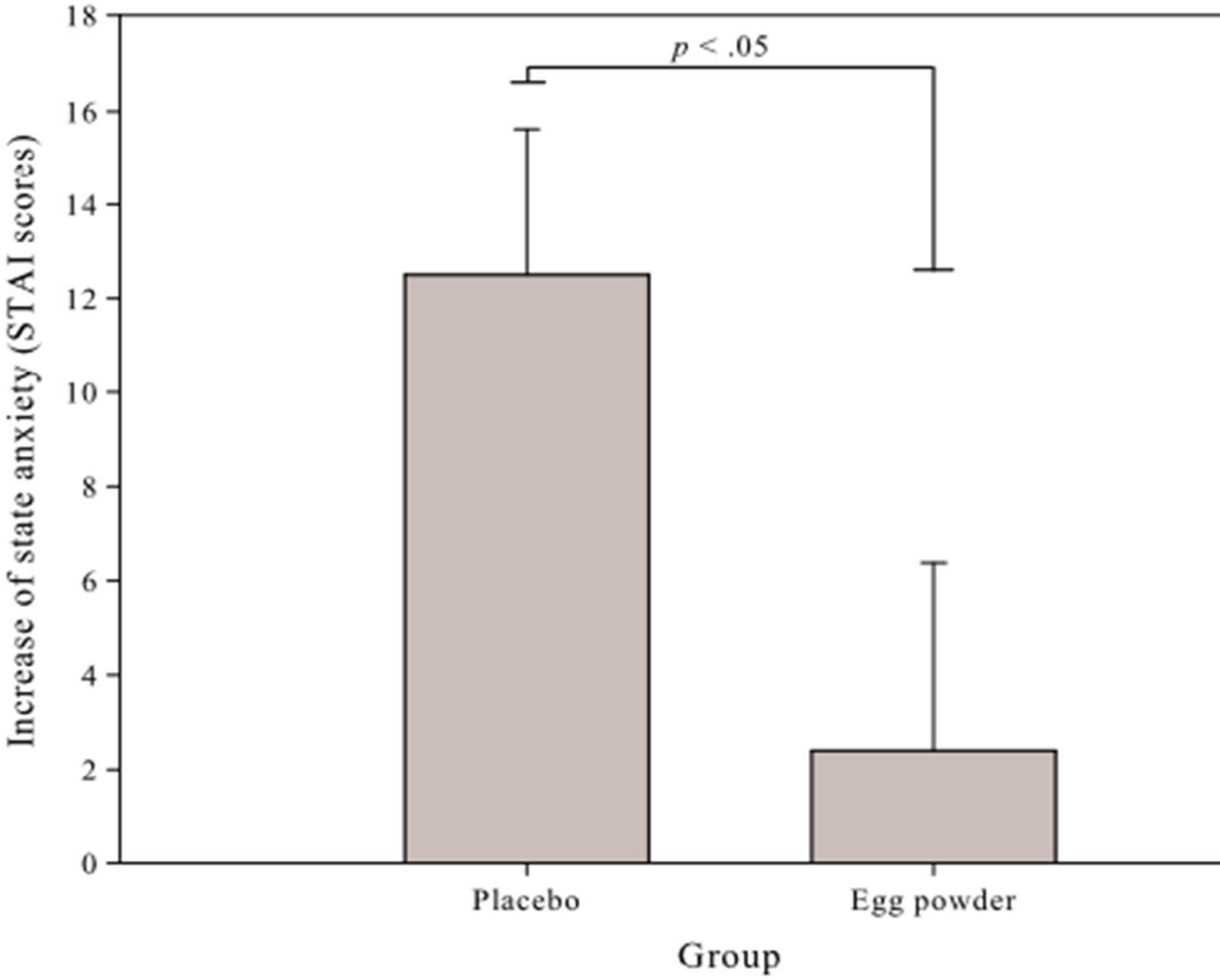


Fig. 4. Increase of state anxiety (STAI) in response to the TSST for the subsample ($n = 20$). The graph shows group means with standard error ba sided *t*-test.

Adpt-Cell Signal- AAE Benefits

Skin/Collagen support

- Improves elastin
- Improves collagen

GUT microbiome

supportive

- Increased microbial diversity
- Increased butyrate prodution

Blood glucose/insulin normalization

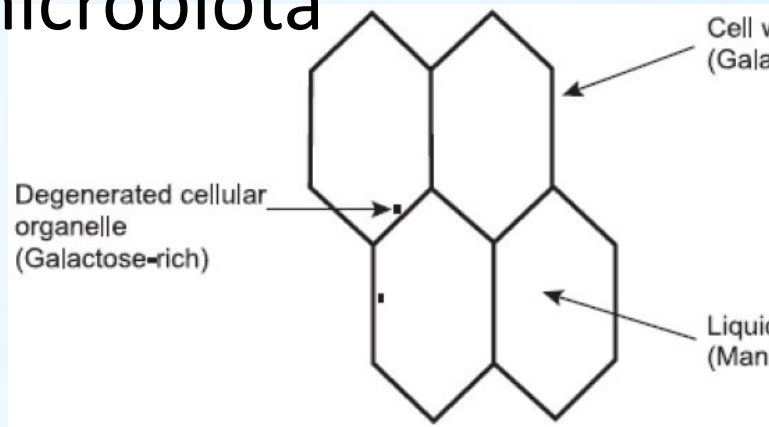
- Human study n=11 reported AEE statistically reduced HgA1c, FBS

Lipid regulation

Schilt J, et al. Effects of powdered fertilized eggs on the stress resp
Nutr. 2010;29(2)(:255-60.

Aloe barbadensis 200:1 extract

- Aloe rich in polysaccharides – prebiotic acemannan
- Helps support GUT mucosa and microbiota
- Antiinflammatory
- Immune modulatory
- Antimicrobial, including antiviral
- Supports GUT – IMMUNE – BRAIN signaling
- Blood glucose regulatory



Hamman JH, et al. Composition and applications of aloe vera leaf gel. Molecu
2008;13(8):1599-1616.

Sunfiber®

- Proprietary – from Guar plant in W. India
- Soluble dietary fiber – hydrolyzed guar gum
- Reported beneficial in preventing cardiovascular diseases
- Prebiotic – produces SCFAs in the GUT
- Supports microbiome and T2 GUT-Immune and T5 estrogen metabolism
- Low FODMAP and gluten free

SunFiber®

- Not reported to impair nutrient/drug absorption
- Supports weight management
- Supports estrogen metabolism in the GUT
- Reduces glycemic index of foods
- Appetite control

SunFiber®

- Tasteless, odorless
- No gas or bloating associated with other fibers
- Supports GUT microbiome – 2019 3 mo. study in 44 healthy subjects

Effect of Repeated Consumption of Partially Hydrolyzed Guar Gum on Fecal Characteristics and Gut Microbiota: A Randomized, Double-Blind, Placebo-Controlled, and Parallel-Group Clinical Trial.

Author: Yasukawa, Z, et al.

Location: Nutrients. 2019 Sep 10;11(9). pii: E2170. doi: 10.3390/nu11092170.

Read Full Study: www.ncbi.nlm.nih.gov

Sunfiber® and Cardiovascular Diseases

- Fiber and Cardiovascular Support studied for decades
- 2017 review of 31 meta-analyses reported dietary fiber intake:
  - Significantly reduces the incidence of cardiovascular disease and cardiovascular disease mortality
  - Also reduces incidence coronary artery disease and stroke
  - Reported to reduce total serum cholesterol and LDL cholesterol levels

McRae MP. Dietary fiber is beneficial for the prevention of cardiovascular disease: an umbrella review of meta-analyses. J Chiropr Med. 2017;16(4):289-99.

Adpt-Cell Signal Dosage

1 scoopful (1.4gm) in smoothie or beverage, 1-3 times daily

4 calories per scoop – 0 sugars, 0.2gm soluble fiber, 0.2gm total carbs

Do not use if allergy to eggs exist

AAE raw material made with proprietary “Cooling Method” so no peptides are destroyed in manufacturing

Curcumin

- From turmeric (*Curcuma longa)* root/rhizome

- Traditionally for dyspeptic conditions

- Curcuminoids reported:
  - Antiinflammatory
  - Decreases inflammasome signaling
  - Supports musculoskeletal system
  - Joints/connective tissue support
  - Helps improve flexibility and mobility

Curcumin - Metaflammation

- Decreases oxidative stress via Nrf2-keap1 pathway
- Inhibits nuclear factor-kappaB
- Inhibits Toll-like receptor 4-dependent signaling pathways
- Inhibits activation of a peroxisome proliferator-activated receptor-gamma pathway.

Castro CN, et al. Curcumin ameliorates autoimmune diabetes,. Evidence in accelerated murine models of type 1 diabetes. Clin Exp Immunol. 2014;177(1):149-60.

Curcumin Metaflammation

- Modulates multiple cell signaling molecules
  - TNF-alpha
  - IL 1, IL-6
  - COX-2 and 5-lipoxygenase
  - NF-kappaB
  - CRP
  - PgE2
  - TGF-beta
  - AST/ALT
  - Malondialdehyde MDA
- Lab study reports curcumin ameliorates pancreatic beta cell destruction in autoimmune diabetes

Castro CN, et al. Curcumin ameliorates autoimmune diabetes,. Evidence in accelerated murine models of type 1 diabetes. Clin Exp Immunol. 2014;177(1):149-60.

Curcumin - Completed Human Clinical trial

ese performed globally with varied
sages and forms – raw herb, standardized
d extracts

- Alzheimer's
- Acute coronary syndrome
- Atherosclerosis
- Diabetes,
- Cancers – colorectal, breast, multiple myeloma, pancreatic, prostate, lung, oral lesions, head/neck squamous cell
- Inflammatory Bowel Diseases (IBDs)
- Osteoarthritis
- Uveitis
- Chronic bacterial prostatitis
- Alcohol intoxication

Gupta SC, et al. AAPS Journal. 2013;15(1):195-206.

- Chronic arsenic exposure
- Recurrent respiratory tract infections
- Postoperative inflammation
- Peptic ulcer/H. pylori infecti
- Idiopathic orbital inflammato pseudotumor
- Vitiligo
- Psoriasis
- Dejerine-Sottas Disease
- Renal transplants
- Lupus nephritis
- AIDS
- Beta-thalassemia
- Biliary dyskinesia, gallbladd contractions

Look

# of Types of rcumin oducts on obal Market Which One choose?

ad S, et al. Cancer Res
t. 2014;46(1):2-18.

Oral, GI Absorbed Curcumin – Dosage

- Oral encapsulated
  - 500-750mg BID-TID of curcuminoids 98%
  - + added Bioperine (extract of black pepper, piperine) for improved bioavailability – NOT OPTIMAL
- Bioavailability of active curcuminoid compounds still suffers -1st pass effect
- Take with food

Prasad S, et al. Cancer Res Treat. 2014;46(1):2-18.

ent Curcumin Headlines....

CHEMICAL BIOLOGY

Curcumin Will Waste Your Time

By Derek Lowe | 12 January, 2017

- Curcuminoids (I, II, and III) are poorly bioavailable orally
  - IV curcumin – Asia, Europe, Central and S. America
  - Topical curcumin
  - Intranasal curcumin
  - Improved oral extractions – 95% curcuminoids + bioperine
  - Water-soluble curcumin
  - Sublingual liposomal curcumin
  - Sublingual nanoparticle curcumin
- Led to development of superior bioavailable and clinically useful curcumin produc an oral nanospray
- SMART technology using safe ingredients for the microbiome

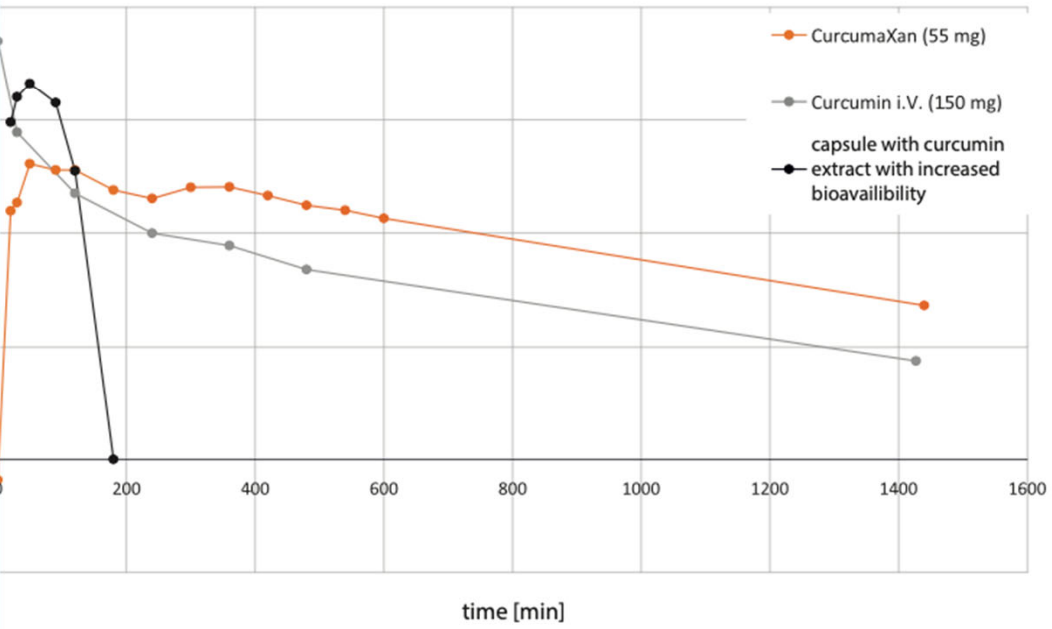
Curcumin - NanoSpray

- 99% curcuminoid oral spray; Curcuminoids I, II and III
- 94% higher absorption than a curcumin capsule with optimized uptake at 1/10 of the dose =
  - 313-fold higher absorption than a curcumin capsule at 3% of the dose
- 410% higher absorption compared to curcumin infusion comparable dose =
  - 50% better absorption than 1/3 of the dose of curcum infusion
- Consistently high level of curcuminoids for daily use at a fraction

Of oral doses

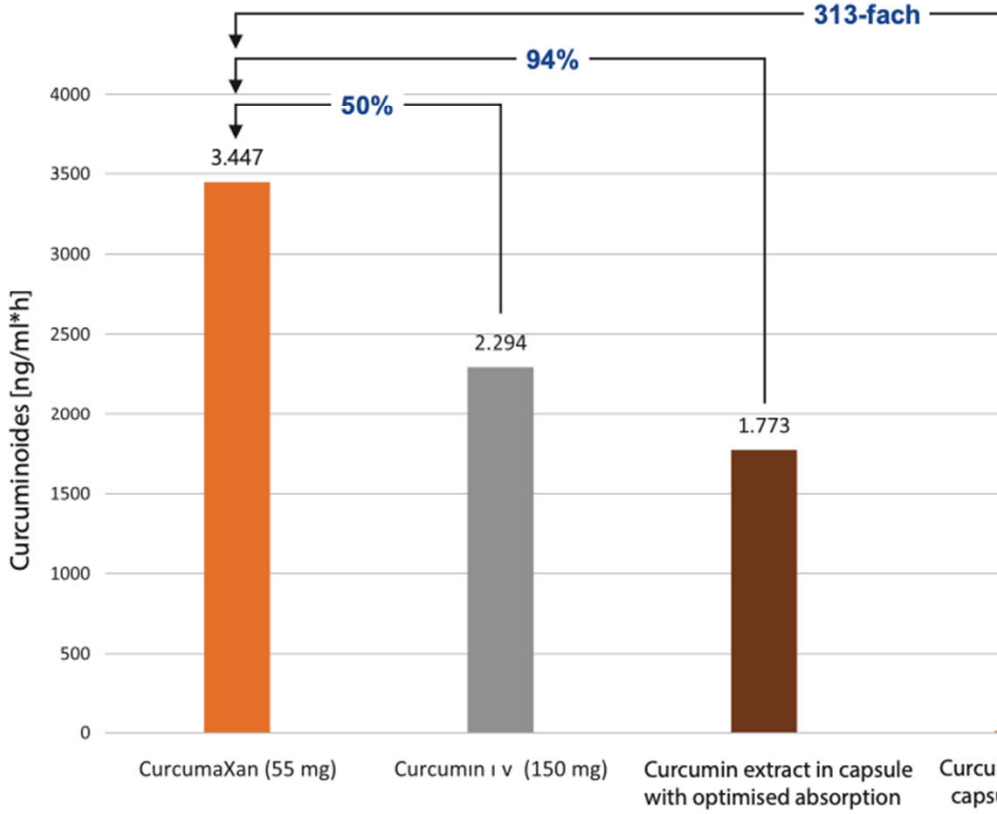
Castro CN, et al. Curcumin ameliorates autoimmune diabetes,. Evidenc accelerated murine models of type 1 diabetes. Clin Exp Immunol. 2014;177(1):149-60.

arison of pharmacokinetics data from CurcumaXan, umin infusion and a curcumin capsule with ised uptake



arison of the pharmacokinetics data of CurcumaXan at of 55 mg curcumin and a curcumin infusion at a dose mg.

AUC values [ng/ml*h] over 24 h of CurcumaXan, a curcumin infusion and curcumin ca



Apurano Pharmaceuticals, Warngau Germany

“Smart Turmeric” Indications

Control meta-inflammatory responses

Osteoarthritis

MetS – insulin/blood glucose,

Cardiovascular support – atherosclerosis;

Exercise recovery

- Oncological indications - cancer
- IBDs - inflammatory bowel diseases
- Postoperative inflammation/pain
- Skin issues – psoriasis, eczema, dermatitis

“Smart Turmeric”– Dosage

Oromucosal Water soluble nanospray

- 9 sprays daily (3 sprays TID) = 42mg

curcuminoids daily total

- 42 mg is bioequivalent to approx. 450mg “regular” 95% curcumin extracts
- EU proprietary formulation
- Improved bioavailability over C3 and other curcumin products
- Stability studies x 2yrs
- Sublingual delivery
- Pharmaceutically manufactured - sterile

Prasad S, et al. Cancer Res Treat. 2014;46(1):2-18.

Curcumin Contraindications/ Side Effects

Studies have assessed safety of doses from 500mg - 12,000 mg

- Transient side effects most common – diarrhea, headache, rash, yellow stool abdominal pain

Potential to increase ALP (alkaline phosphatase) & LD (lactate dehydrogenase)

As per German Commission E monographs:

Turmeric should not be used in biliary obstruction

Curcuminoids are reported to have biliary stimulatory activity

Gupta SC, et al. AAPS Journal. 2013;15(1):195-206.