From Common to Complex, Part 2

Hormones, Therapeutics, Metabolic Optimization: From Assessment to Targeted Intervention

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Disclaimer

We take pride in presenting the most current research, literature, and clinical observations available. However, the information provided herein has not been evaluated or approved by the U.S. Food and Drug Administration (FDA) or any of its affiliates. While every effort has been made to cite appropriate sources, some references may inadvertently be missing.

All dosage recommendations are intended for adults. As with any therapeutic intervention, treatments should be undertaken only under the supervision of a licensed physician. We strongly advise against altering, reducing, or discontinuing any prescribed medication or nutritional therapy without first consulting the prescribing clinician.

Although we strive to present information accurately and in alignment with published data or clinical experience, we acknowledge that human error is possible. Therefore, we encourage independent confirmation of any details prior to application.

This material is provided for educational purposes only and is not intended to substitute for professional medical advice, diagnosis, or treatment.

Today's Presentation

clinical pearl (*ˈkli-ni-kəl pərl) noun*

- **Medicine.** A concise, experience-based insight that conveys practical clinical wisdom, often derived from repeated patient encounters rather than formal study. Clinical pearls emphasize pattern recognition, efficiency, and real-world applicability in diagnosis, treatment, or patient management.
- **Usage.** Typically shared in teaching rounds, lectures, or professional writing to distill complex concepts into memorable, actionable guidance.

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01

CLINICAL PEARL: ANTI-NUCLEAR ANTIBODY TESTING

Anti-Nuclear Antibody Testing

ANA by IFA (Indirect Immunofluorescence)

- Uses whole cells (typically HEp-2 cells)
- Detects **any antibodies that bind to nuclear structures**
- Very **sensitive** (picks up a wide range of antibodies)
- Provides **patterns** (homogeneous, speckled, nucleolar, etc.)
- Semi-quantitative (titers)

Clinical Pearl: **Broad screening test**

ANA "Direct" (often ELISA or multiplex)

- Uses **specific purified antigens** (dsDNA, Sm, RNP, SSA, SSB, etc.)
- Detects **only predefined antibodies**
- More **specific**, but less sensitive
- No pattern information

Clinical Pearl: **More targeted antibody panel**

Anti-Nuclear Antibody Testing

IFA amplifies weak binding visually

ELISA/multiplex (Direct) requires stronger, more specific binding

ANA IFA = positive (especially low titers like 1:40–1:80)

ANA Direct = negative

Date Collected: **02/25/2026** Date Received: **02/26/2026** Date Reported: **02/27/2026** Fasting: **No**

Ordered Items: **Iron and TIBC; Vitamin D, 25-Hydroxy; Ferritin; ANA by IFA Rfx Titer/Pattern**

Ferritin

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Ferritin [01]	22	**10** 10/24/2025	ng/mL	15-150

ANA by IFA Rfx Titer/Pattern

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▶ **ANA by IFA Rfx Titer/Pattern** [02]	**Positive** **Abnormal**	**Positive** 10/24/2025		Negative <1:80 Borderline 1:80 Positive >1:80
Homogeneous Pattern [02]	1:80 TCAP nomenclature: AC-1	1:80 10/24/2025		

Date Collected: **03/24/2026** Date Received: **03/25/2026** Date Reported: **03/25/2026** Fasting: **No**

Ordered Items: **LUPUS PROFILE**

Date Collected: **03/24/2026**

LUPUS PROFILE

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
RNP Antibodies [01]	<0.2		AI	0.0-0.9
Smith Antibodies [01]	<0.2		AI	0.0-0.9
Anti-DNA (DS) Ab Qn [01]	<1		IU/mL Negative <5 Equivocal 5 - 9 Positive >9	0-9
ANA Direct [01]	Negative			Negative

Previous Result

Anti-Nuclear Antibody Testing

IFA positivity (especially low titer) can occur with:

- Aging
- Infections
- Chronic inflammation
- Even healthy individuals (~10–20% low-titer positivity)

Date Collected: **03/02/2026** Date Received: **03/03/2026** Date Reported: **03/05/2026** Fasting: **No**

Ordered Items: **ANA by IFA Rfx Titer/Pattern**

Date Collected: **03/02/2026**

ANA by IFA Rfx Titer/Pattern

Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▶ **ANA by IFA Rfx Titer/Pattern** [01]	**Positive**	**Abnormal**	**Positive** 09/16/2025		Negative <1:80 Borderline 1:80 Positive >1:80
▲ **Speckled Pattern** [01]	**1:320** ICAP nomenclature: AC-2,4,5,29	**High**	**1:320** 09/16/2025		
▲ **Nuclear Dot Pattern** [01]	**1:320** ICAP nomenclature: AC-6,7	**High**			

Date Collected: **03/19/2026** Date Received: **03/20/2026** Date Reported: **03/21/2026** Fasting: **No**

Ordered Items: **LUPUS PROFILE**

Date Collected: **03/19/2026**

LUPUS PROFILE

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
RNP Antibodies [01]	<0.2		AI	0.0-0.9
Smith Antibodies [01]	<0.2		AI	0.0-0.9
Anti-DNA (DS) Ab Qn [01]	2		IU/mL Negative <5 Equivocal 5 - 9 Positive >9	0-9
ANA Direct [01]	Negative			Negative

02

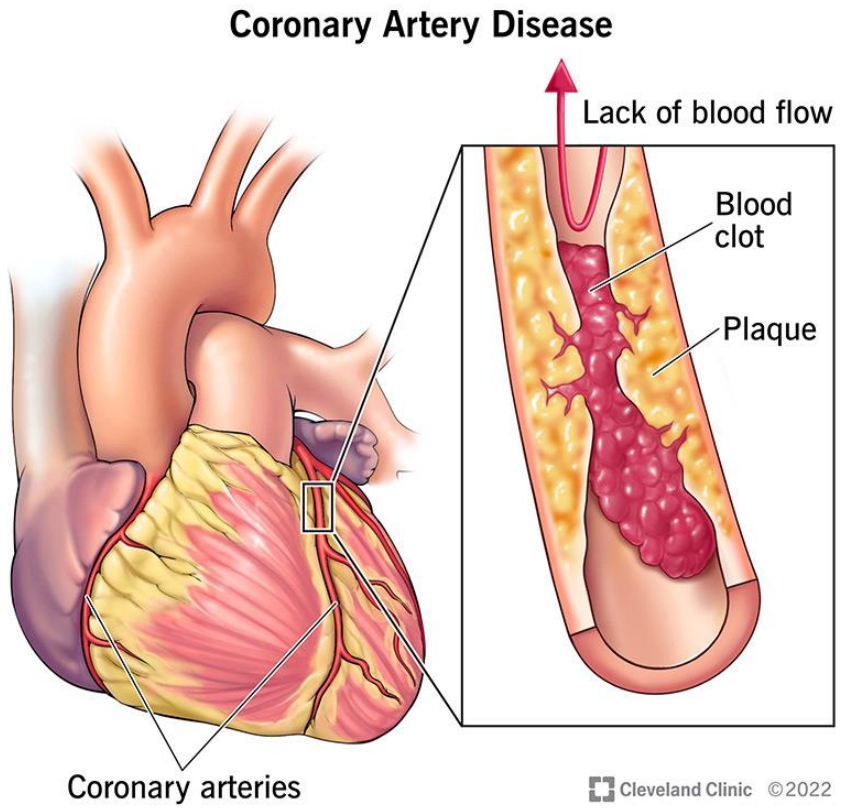
CARDIOMETABOLIC DISEASE

Cardiovascular Disease

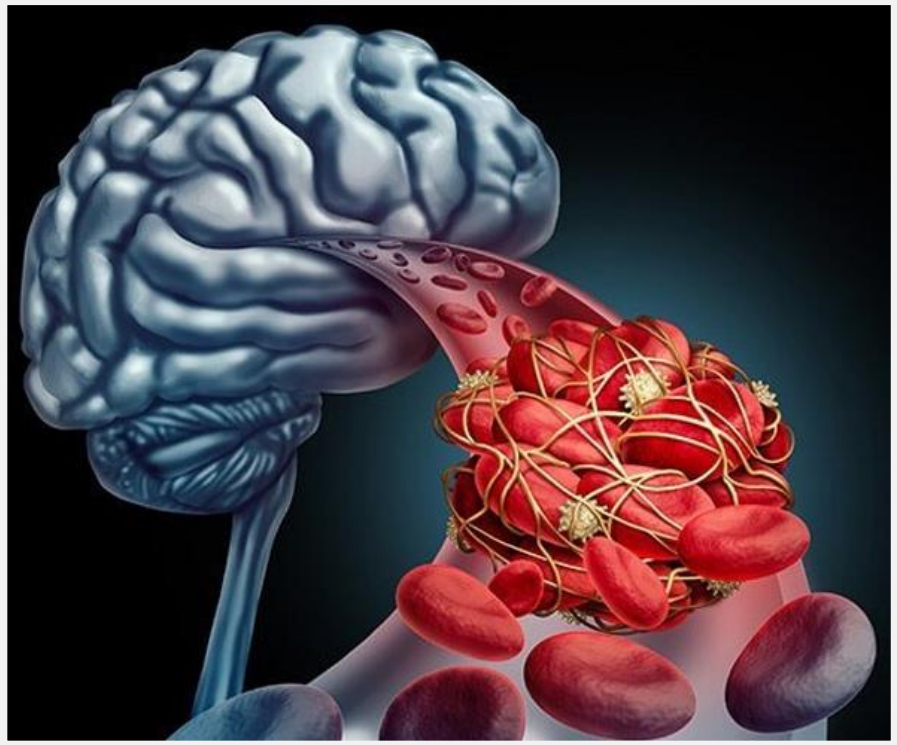
In 2023, 919,032 people in the U.S. died from cardiovascular disease, which was about **1 in every 3 deaths**.

The CDC also notes that **one person dies every 34 seconds** from CVD.

National Center for Health Statistics. Multiple Cause of Death 2018–2023 on CDC WONDER Database.



Cardiovascular Disease and Dementia



According to the American Heart Association:

- Adults with coronary heart disease have about a **27% higher risk of dementia**
- People with **atrial fibrillation** have about a **39% increased risk of cognitive impairment**
- **14%–81%** of patients with **heart failure** show some degree of cognitive impairment.

The statement also notes that **up to 50%** of people can experience cognitive decline after a **heart attack**.

https://newsroom.heart.org/news/heart-failure-atrial-fibrillation-coronary-heart-disease-linked-to-cognitive-impairment

The Brain is a Vascular Organ

The brain receives **~20% of cardiac output.**

Contains **400 miles of microvasculature**

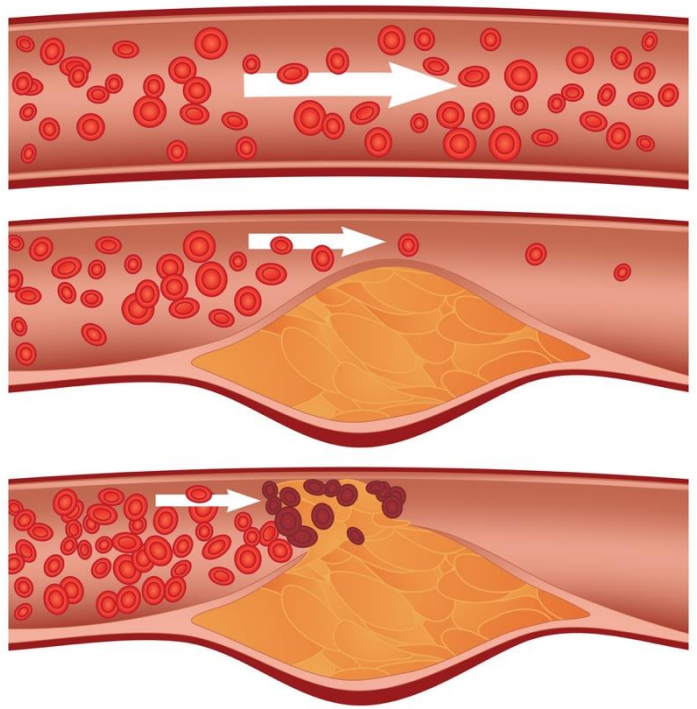
Extremely sensitive to **oxidative stress** and **endothelial dysfunction**

Clinical Implication → Small vessel disease is one of the largest drivers of cognitive decline

Lipid Testing: Pre-Testing Rules

Might postpone testing if:

- You Are Currently Sick
- You Recently Had Surgery or an Acute Injury
- You Are Under Significant Acute Stress
- You Just Started or Changed Hormonal Therapy
- You Recently Had a Heart Attack or Stroke
- You Are Pregnant or Immediately Postpartum
- You Recently Had Significant Weight Change
- You were celebrating – birthday weekend, end of year holidays



Common Cardiovascular Blood Panels

Cardiometabolic Basic

- Lipid Fractionation
- Lp(a)
- Apolipoprotein B
- Hs-CRP
- Homocysteine
- Fibrinogen

Cardiometabolic Expanded

- Lipid Fractionation
- Lp(a)
- Apolipoprotein B
- Ox-LDL
- ApoA1
- GlycA
- Hs-CRP
- Myeloperoxidase
- Homocysteine
- ADMA/SDMA
- Uric Acid
- Fibrinogen
- HbA1c
- Insulin
- Adiponectin
- Lp-PLA2

Hypertension

- ADMA/ SDMA
- Renin/Aldosterone
- Ox-LDL
- Myeloperoxidase
- GlycA
- Homocysteine

Additional Diagnostics: Carotid IMT, ABI, Cardiac CT, Stress Test, EKG, Echo, ….

“Free” Diagnostic: Early Warning Signs

European Heart Journal (2006) 27, 2632–2639
doi:10.1093/eurheartj/ehl142

Clinical research
Coronary heart disease

Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial

Piero Montorsi[1]*, Paolo M. Ravagnani[1], Stefano Galli[1], Francesco Rotatori[1], Fabrizio Veglia[1], Alberto Briganti[2], Andrea Salonia[2], Federico Dehò[2], Patrizio Rigatti[2], Francesco Montorsi[2], and Cesare Fiorentini[1]

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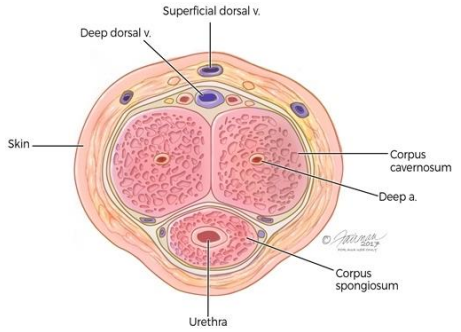
Received 15 December 2005; revised 10 May 2006; accepted 14 June 2006; online publish-ahead-of-print 19 July 2006

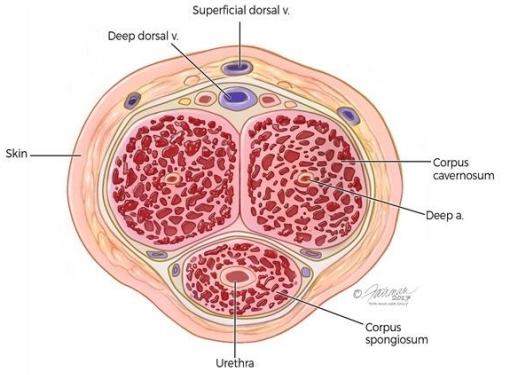
See page 2613 for the editorial comment on this article (doi:10.1093/eurheartj/ehl110)

KEYWORDS
Erectile dysfunction;
Coronary artery disease;
Acute coronary syndrome;
Gensini's score;
Chronic coronary syndrome

Aims To investigate the p
cal presentation, acute
vessel involvement (sing
Methods and results 28
n = 95), ACS and one-v
n = 95), chronic CS. Co
were found to have ent
extent of CAD. ED as an
ED prevalence was lowe
burden as expressed by
values similar to G1 (24
from G1 [55%, *P* < 0.0
suggesting that despite
CAD. No significant diffe
factors. Treatment with
had ED, onset of sexual
24 [12–36] months. In
1.05–1.16; *P* = <0.0001
and CCS vs. ACS (OR = 2
Conclusion ED prevalenc
presentation and extent
by an average of 2 up to 3 years.



FLACCID



ERECT

In a sub study of **1549** men with CVD who participated in the ONTARGET and TRANSCEND trials, men with ED (compared to those without ED) were **twice as likely to suffer death from all causes** and **1.6 times more likely to suffer the composite of cardiovascular death, heart attack, stroke, or heart failure hospitalization** during follow-up (median, 53–54 months).

Erectile Dysfunction and Risk of Cardiovascular Disease

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ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.06.024

Cardiovascular Risk

Erectile Dysfunction and Risk of Cardiovascular Disease

Meta-Analysis of Prospective Cohort Studies

Jia-Yi Dong, BSc,* Yong-Hong Zhang, MD, PhD,† Li-Qiang Qin, MD, PhD*
Suzhou, China

Objectives Our goal was to evaluate the association between erectile dysfunction (ED) and risk of cardiovascular disease (CVD) and all-cause mortality by conducting a meta-analysis of prospective cohort studies.

Background Observational studies suggest an association between ED and the incidence of CVD. However, whether ED is an independent risk factor of CVD remains controversial.

Methods The PubMed database was searched through January 2011 to identify studies that met pre-stated inclusion criteria. Reference lists of retrieved articles were also reviewed. Two authors independently extracted information on the designs of the studies, the characteristics of the study participants, exposure and outcome assessments, and control for potential confounding factors. Either a fixed- or a random-effects model was used to calculate the overall combined risk estimates.

Results Twelve prospective cohort studies involving 36,744 participants were included in the meta-analysis. The overall combined relative risks for men with ED compared with the reference group were 1.48 (95% confidence interval [CI]: 1.25 to 1.74) for CVD, 1.46 (95% CI: 1.31 to 1.63) for coronary heart disease, 1.35 (95% CI: 1.19 to 1.54) for stroke, and 1.19 (95% CI: 1.05 to 1.34) for all-cause mortality. Sensitivity analysis restricted to studies with control for conventional cardiovascular risk factors yielded similar results. No evidence of publication bias was observed.

Conclusions This meta-analysis of prospective cohort studies suggests that ED significantly increases the risk of CVD, coronary heart disease, stroke, and all-cause mortality, and the increase is probably independent of conventional cardiovascular risk factors. (J Am Coll Cardiol 2011;58:1378–85) © 2011 by the American College of Cardiology Foundation

Erectile dysfunction (ED) is common and increases as men age. It is estimated that approximately 18 million men in United States currently experience ED (1). Meanwhile, cardiovascular disease (CVD) remains the leading cause of death in the United States (2). It is well accepted that CVD predicts incidence of ED, largely because both conditions share the same risk factors, including age, hypertension, dyslipidemia, smoking, obesity, and diabetes (3). Conversely, it has also been hypothesized that ED may be a marker of further cardiovascular events (4).

The past few years have seen a rapidly growing interest in testing this hypothesis. Many epidemiologic studies (5–21) have investigated the link between ED and risk of CVD, and most found a positive association. However, the magnitudes of the association varied between studies. Although a previous meta-analysis (22) combined several cohort studies and reported a statistically significant relation of ED to cardiovascular risk, evidence was limited because only 7 cohort studies were available at that time. Of note, 2 of the 7 cohort studies used a retrospective cohort design, which suffers more confounding and biases than a prospective cohort design. Furthermore, whether ED is an independent risk factor or merely a silent marker of CVD remains unclear. An improved understanding of this issue may have important public health and clinical implications given the possibility that prevention and treatment of ED might reduce the incidence of cardiovascular events. With recently accumulating evidence, our goal, therefore, was to evaluate the association between ED and risk of CVD and all-cause mortality by conducting a meta-analysis of prospective cohort studies.

Methods

Search strategy. We attempted to follow the proposed MOOSE (Meta-Analysis of Observational Studies in Epidemiology) (23) guidelines to report the present meta-analysis. We conducted a PubMed database search through January 2011 for relevant studies that tested the association between ED and risk of CVD, coronary heart disease

From the *Department of Nutrition and Food Hygiene, School of Radiation Medicine and Public Health, Soochow University, Suzhou, China; and the †Department of Epidemiology, School of Radiation Medicine and Public Health, Soochow University, Suzhou, China. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received February 25, 2011; revised manuscript received June 2, 2011, accepted June 7, 2011.

A large meta-analysis of **92,000+ men from 14 studies** found men with ED had significantly higher cardiovascular risk:

- **44% increased risk of cardiovascular events**
- **62% increased risk of myocardial infarction**
- **39% increased risk of stroke**
- **25% increased risk of all-cause mortality**

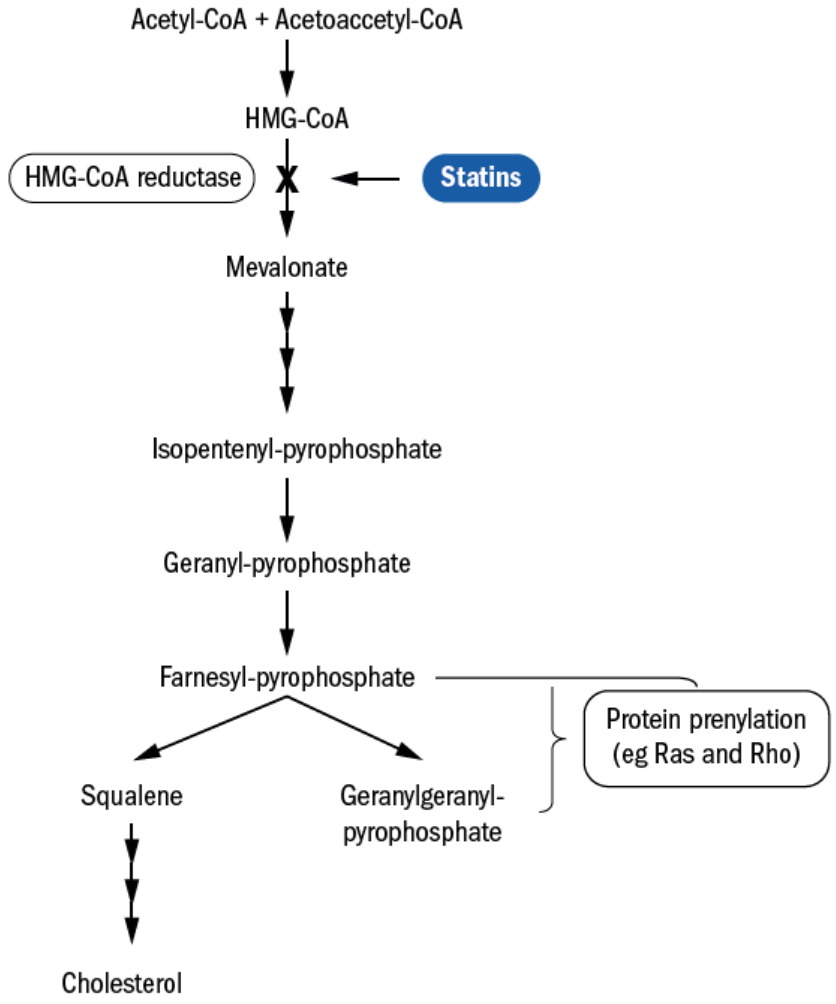
ED frequently appears **before overt cardiovascular disease**

- **ED precedes coronary artery disease by ~3–5 years**
- **ED precedes major cardiovascular events by ~2–3 years**

Eur Urol. 2003 Sep;44(3):352-4.

Statins and Testosterone

- Statin therapy **lowers testosterone** (~10–20%)
- Testosterone supports **HDL-mediated reverse cholesterol transport** and macrophage cholesterol efflux.
- Low testosterone is common in **heart failure** and predicts **increased mortality (~10–11% per 10 ng/dL drop)**.



Circulation. 2006;114(17):1829-1837.doi:10.1161/CIRCULATIONAHA.106.649426
J Urol. 2010;76(5):1048.
Annu Rev Med. 2003;54:321-340.
J Clin Endocrinol Metab. 2013;98(7):2725-2732. doi:10.1210/jc.2013-1220
BJU Int. 2010;106(8):1171-1175. doi:10.1111/j.1464-410X.2010.09328.x
J Sex Med. 2015;12(5):1036-1047. doi:10.1111/jsm.12836
Heart. 2010;96(22):1821-1825. doi:10.1136/hrt.2009.179382
Heart. 2006;92(7):900-905. doi:10.1136/hrt.2005.074773

CoQ10: Red Yeast Rice (RYR) v. Statin

CoQ10 is recommended during long term usage of RYR, just like statin medication

RYR → Monacolin K directly inhibits HMG-CoA reductase

- RYR treatment LDL reduction 21-17%
  - Plasma CoQ10 reduction 7-12%
  - Rarely reported myopathy
- Mean **plasma CoQ10 decreased ~16–54%** depending on statin potency and dose

Pharmacol Res. 2015 Sep;99:329-36. Epub 2015 Jul 17.

Red yeast rice for dyslipidemia in statin-intolerant patients. Annals of Internal Medicine. 2009.
Cicero AFG, Derosa G, Parini A, et al. *Red yeast rice improves lipid profile without affecting coenzyme Q10 levels in moderately hypercholesterolemic subjects.* Lipids in Health and Disease. 2013.

54yo Male; Rosuvastatin 10mg for 20+ years

Date Collected: **04/07/2026**

NMR LipoProfile+Lipids+IR+Gph

Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲ **LDL-C (NIH Calc)** [01]	**178**	**High**		mg/dL	0-99
HDL-C [A, 01]	45			mg/dL	>39
▲ **Triglycerides** [A, 01]	**198**	**High**		mg/dL	0-149
▲ **Cholesterol, Total** [A, 01]	**260**	**High**		mg/dL	100-199

Risk Categories	Adult Lipids (mg/dL) LDL-c	Trig	Children Lipids (mg/dL) 2-19 yrs Chol	0-9 yrs LDL-c	10-19 yrs Trig	Trig
Optimal	<100	<150	<170	<110	<75	<90
Near Optimal	100-129					
Borderline	130-159	150-199	170-199	110-129	75-99	90-129
High	160-189	200-499	>199	>129	>99	>129
Very High	>189	>499				

Lipoprotein (a)

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Lipoprotein (a) [A, 01]	20.7		nmol/L	<75.0

Concentration	Risk
<75 nmol/L	Low Lp(a)-attributable ASCVD risk
75 - <125 nmol/L	Intermediate Lp(a)-attributable ASCVD risk
>=125 nmol/L	High Lp(a)-attributable risk, with increasing risk with higher Lp(a) values

Lp-PLA2 Activity

Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval	rence Interval
▲ **Lp-PLA2 Activity** [01]	**234**	**High**		nmol/min/mL	0-224	10-170
			Reduced Risk	<225		
			Increased Risk	>224		

Homocyst(e)ine

Test	Current Result and Flag	Previous Result and Date		Units	Reference Interval
Homocyst(e)ine [02]	8.1	9.0	01/24/2022	umol/L	0.0-14.5

Date Collected	Date Entered	Date and Time Reported	Physician ID & Name	Page Number
04/07/2026	04/08/2026	04/09/2026 06:48 PM ET	1962845149 - WISNIEWSK, B	2 of 2

PARTICLE CONCENTRATION AND SIZE

❖ LDL and HDL Particles

Lower CVD Risk — Higher CVD Risk

Percentile in Reference Population①

		high	75th	50th	25th	low
HDL-P (total)	µmol/L 35.7		34.9	30.5	26.7	

		low	25th	50th	75th	high
SMALL LDL-P	nmol/L 1411		117	527	839	

LDL SIZE	nm 19.8	23.0	Large (Pattern A)	20.6	20.5 Small (Pattern B)	19.0

Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account.

LipoProtein Markers Associated with Insulin Resistance & Diabetes Risk②③

Insulin Sensitive — Insulin Resistant

Percentile in Reference Population①

		low	25th	50th	75th	high
LARGE VLDL-P	nmol/L 5.1		0.9	2.7	6.9	
SMALL LDL-P	nmol/L 1411		117	527	839	

		high	75th	50th	25th	low
LARGE HDL-P	µmol/L 5.5		7.3	4.8	3.1	

		small	25th	50th	75th	large
VLDL SIZE	nm 43.3		42.4	46.6	52.5	

		large	75th	50th	25th	small
LDL SIZE	nm 19.8		21.2	20.8	20.4	
HDL SIZE	nm 9.4	large	75th	50th	25th	small
			9.6	9.2	8.9	

Insulin Resistance Score

		insulin sensitive	25th	50th	75th	insulin resistant
LP-IR SCORE**	0-100 49		27	45	63	

Normal weight
Zone 2-3 cardio everyday
Weight lifts 4x per week
80% of the time→ whole food diet

56yo Male; Firefighter Hx of MI

Complaints: 2020 Heart attack (misdiagnosed as acid reflux)- 2 stents placed (LAD and circumflex), low testosterone, low energy, low thyroid (Rx), frequent wintertime illness

Goes to a “preventative” Cardiology Clinic
His doctor wants his LDL to be below 70mg/dL
→ Praluent (alirocumab) injectable medication (PCSK9 inhibitor)
They are currently happy with his progress

NMR LipoProfile+Lipids+IR+Gph

Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
LDL-C (NIH Calc)[01]	71			mg/dL	0-99

Risk Categories	Adult Lipids (mg/dL) LDL-c	Adult Lipids (mg/dL) Trig	Children Lipids (mg/dL) 2-19 yrs Chol	Children Lipids (mg/dL) 2-19 yrs LDL-c	Children Lipids (mg/dL) 0-9 yrs: 10-19 yrs Trig
Optimal	<100	<150	<170	<110	<75 : <90
Near Optimal	100-129				
Borderline	130-159	150-199	170-199	110-129	75-99 : 90-129
High	160-189	200-499	>199	>129	>99 : >129
Very High	>189	>499			

▼	**HDL-C**[A,01]	**32**	**Low**		mg/dL	>39
▲	**Triglycerides**[A,01]	**202**	**High**		mg/dL	0-149
	Cholesterol, Total[A,01]	137			mg/dL	100-199

Date Collected	Date Entered	Date and Time Reported	Physician ID & Name	Page Number
03/19/2026	03/19/2026	03/22/2026 02:44 PM ET	1962845149 - WISNIEWSK, B	2 of 2

PARTICLE CONCENTRATION AND SIZE

❖ **LDL and HDL Particles**

Lower CVD Risk ← Higher CVD Risk
Percentile in Reference Population①

		high	75th	50th	25th	low
HDL-P (total)	µmol/L 28.5		34.9	30.5	26.7	

		low	25th	50th	75th	high
SMALL LDL-P	nmol/L 674		117	527	839	

LDL SIZE	nm 19.7	23.0	Large (Pattern A)	20.6	20.5 Small (Pattern B)	19.0

Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account.

LipoProtein Markers Associated with Insulin Resistance & Diabetes Risk②③

Insulin Sensitive ← Insulin Resistant
Percentile in Reference Population①

		low	25th	50th	75th	high
LARGE VLDL-P	nmol/L 5.8		0.9	2.7	6.9	
SMALL LDL-P	nmol/L 674		117	527	839	

		high	75th	50th	25th	low
LARGE HDL-P	µmol/L 2.3		7.3	4.8	3.1	

		small	25th	50th	75th	large
VLDL SIZE	nm 48.2		42.4	46.6	52.5	
LDL SIZE	nm 19.7	large	75th	50th	25th	small
			21.2	20.8	20.4	
HDL SIZE	nm 8.6	large	75th	50th	25th	small
			9.6	9.2	8.9	

Insulin Resistance Score

		insulin sensitive	25th	50th	75th	insulin resistant
LP-IR SCORE**	0-100 76		27	45	63	

CV Events and Cardiovascular Blood Markers

Marker	Relative Risk Increase
LDL Particle Number (LDL-P)	↑ 1.4×
Small LDL Subclass Particles	↑ 1.3×
Medium LDL Subclass Particles	↑ 1.4×
HDL Subclasses (Dysfunctional HDL)	↑ 1.8×
Lipoprotein(a) [Lp(a)]	↑ 1.5 – 5.3×
Apolipoprotein B (ApoB)	↑ 2.0 – 2.5×
hs-CRP	↑ 1.5 – 2.0×
Lp-PLA$_2$ (PLAC®)	↑ 1.7 – 2.9× (CVD) ↑ 1.9 – 11.4× (Stroke)

~40-50% of patients presenting to an ER for a cardiovascular event have an **LDL <100mg/dL**

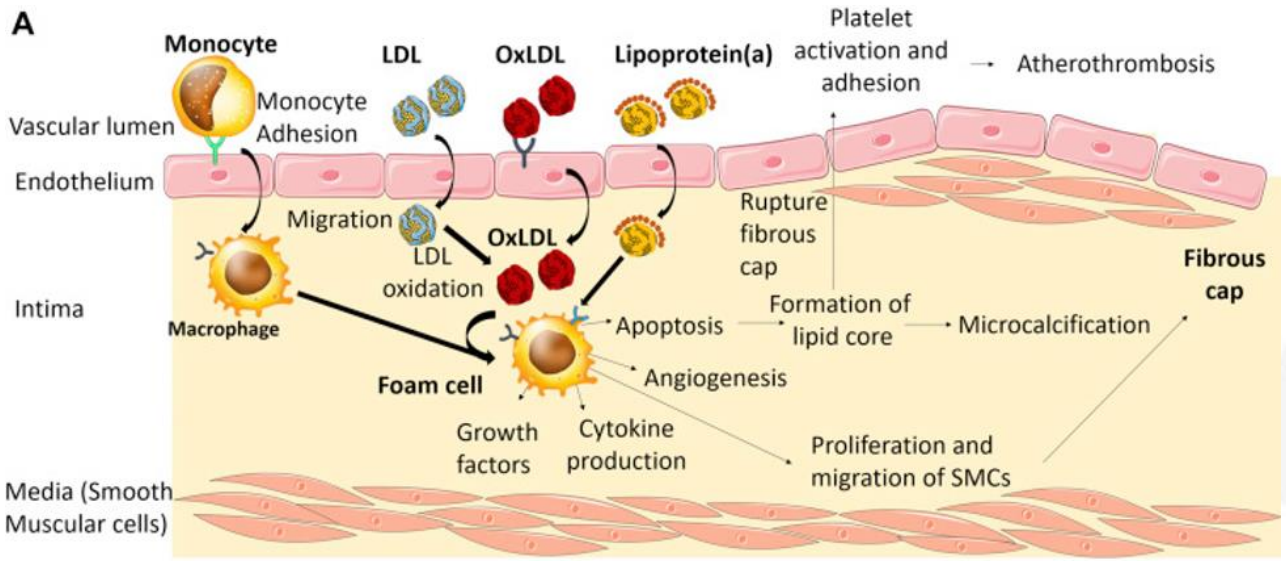
~30% of this population has LDL cholesterol **<70mg/dL**

Arterioscler Thromb Vasc Biol. 2009;29:1975–80
J Clin Lipidol. 2012;6:496–523
Eur Heart J. 2010;31:2844–53
Circ Cardiovasc Qual Outcomes. 2011;4:337–45
N Engl J Med. 2002;347:1557–65
Circulation. 2004;109:837–42
Arch Intern Med. 2005;165:2479–84

Oxidized LDL (ox-LDL)

Elevated ox-LDL → 2- to 4-fold increased risk of coronary artery disease
Acute coronary syndrome → ox-LDL levels were ~3× higher than in healthy controls.

Oxidized LDL (ox-LDL) is low-density lipoprotein cholesterol that has undergone **oxidative modification** → active vascular injury



- Macrophages engulf it via scavenger receptors
- Foam cells accumulate in artery walls
- Stimulates cytokine release
- Activates endothelial dysfunction
- Increases adhesion molecules
- Promotes vascular stiffness
- Increases thrombosis risk

Atherosclerosis. 2003;166:163-168
Circulation. 2001;103:1955-1960

oxLDL: Patient Case 52YO Male

Ordered Items: **NMR LipoProfile+Lipids+IR+Gph; Oxidized LDL**

Date Collected: **01/15/2026**

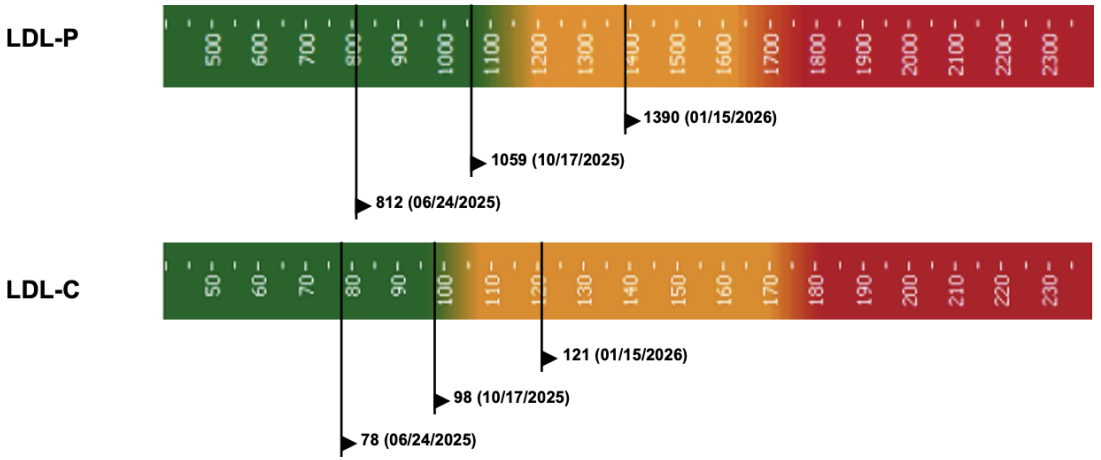
NMR LipoProfile+Lipids+IR+Gph

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ **LDL-C (NIH Calc)** [01]	**121** **High**	98 10/17/2025	mg/dL	0-99
		Optimal	< 100	
		Above optimal	100 - 129	
		Borderline	130 - 159	
		High	160 - 189	
		Very high	> 189	
HDL-C [A, 01]	43	43 10/17/2025	mg/dL	>39
Triglycerides [A, 01]	84	106 10/17/2025	mg/dL	0-149
Cholesterol, Total [A, 01]	180	160 10/17/2025	mg/dL	100-199

Oxidized LDL

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Oxidized LDL [01]	20	151 07/07/2025	ng/mL	10-170

Historical Reporting



Ran labs right after holidays- less exercise, more alcohol and higher calorie intake

oxLDL 151 → 20 ☺
LDL 98 → 121
LDL-P 1059 → 1390

Direct Cardio Support:
Omega 3 Pro-Resolvins: 1 per day

oxLDL: Patient Case 61YO Female

Date Collected: **12/08/2025** Date Received: **12/09/2025** Date Reported: **12/11/2025** Fasting: **Yes**

Ordered Items: **Oxidized LDL; Lipoprotein (a); C-Reactive Protein, Cardiac; Insulin**

Date Collected: **12/08/2025**

Oxidized LDL

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Oxidized LDL [01]	168	**861** 09/22/2025	ng/mL	10-170

Lipoprotein (a)

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Lipoprotein (a) [A, 01]	59.6	**164.6** 09/22/2025	nmol/L	<75.0

Note: Values greater than or equal to 75.0 nmol/L may indicate an independent risk factor for CHD, but must be evaluated with caution when applied to non-Caucasian populations due to the influence of genetic factors on Lp(a) across ethnicities.

C-Reactive Protein, Cardiac

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ **C-Reactive Protein, Cardiac** [02]	**4.17** **High**	**5.69** 09/22/2025	mg/L	0.00-3.00

Relative Risk for Future Cardiovascular Event
Low <1.00
Average 1.00 - 3.00
High >3.00

Insulin

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ **Insulin** [02]	**39.4** **High**	**26.9** 09/22/2025	uIU/mL	2.6-24.9

Treatment (3 months)

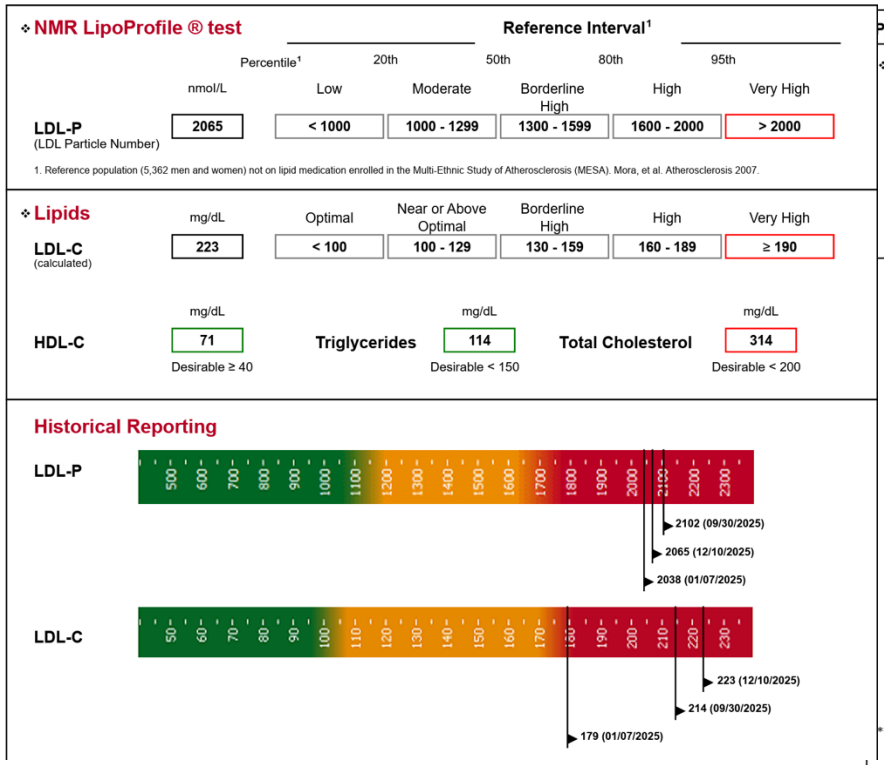
- Combination Cardio Specific Product: 2 b.i.d.

Example list of Ingredients:

- Red Yeast Rice
- Plant Sterols
- Aged Garlic
- Berberine
- Vitamin E

Lipid Fractionation: Patient Case

12.2025



❖ NMR LipoProfile ® test — Reference Interval[1]

	nmol/L	Percentile[1] Low	20th Moderate	50th Borderline High	80th High	95th Very High
LDL-P (LDL Particle Number)	2065	< 1000	1000 - 1299	1300 - 1599	1600 - 2000	> 2000

1. Reference population (5,362 men and women) not on lipid medication enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). Mora, et al. Atherosclerosis 2007.

❖ Lipids

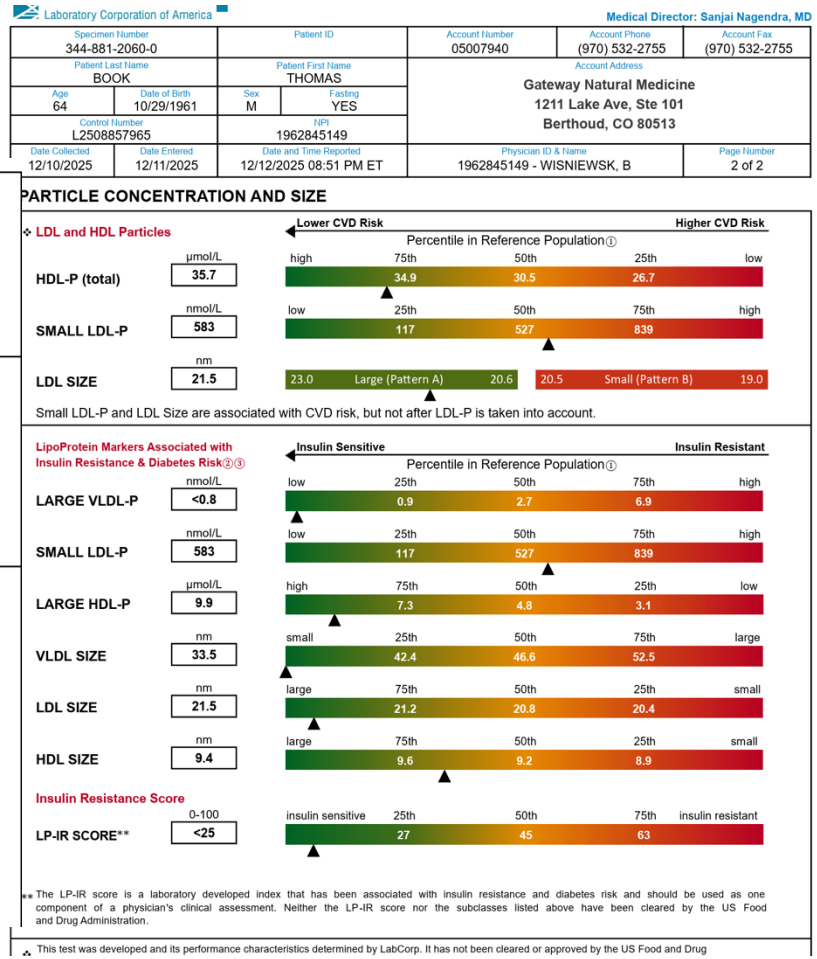
	mg/dL	Optimal	Near or Above Optimal	Borderline High	High	Very High
LDL-C (calculated)	223	< 100	100 - 129	130 - 159	160 - 189	≥ 190

HDL-C	Triglycerides	Total Cholesterol
71 mg/dL	114 mg/dL	314 mg/dL
Desirable ≥ 40	Desirable < 150	Desirable < 200

Historical Reporting

LDL-P: 2102 (09/30/2025); 2065 (12/10/2025); 2038 (01/07/2025)

LDL-C: 223 (12/10/2025); 214 (09/30/2025); 179 (01/07/2025)



Laboratory Corporation of America — Medical Director: Sanjai Nagendra, MD

Specimen Number	Patient ID	Account Number	Account Phone	Account Fax
344-881-2060-0		05007940	(970) 532-2755	(970) 532-2755

Patient Last Name	Patient First Name	Account Address
BOOK	THOMAS	Gateway Natural Medicine 1211 Lake Ave, Ste 101 Berthoud, CO 80513

Age	Date of Birth	Sex	Fasting
64	10/29/1961	M	YES

Control Number	NPI
L2508857965	1962845149

Date Collected	Date Entered	Date and Time Reported	Physician ID & Name	Page Number
12/10/2025	12/11/2025	12/12/2025 08:51 PM ET	1962845149 - WISNIEWSK, B	2 of 2

PARTICLE CONCENTRATION AND SIZE

❖ LDL and HDL Particles — Lower CVD Risk ← Percentile in Reference Population① → Higher CVD Risk

		high	75th	50th	25th	low
HDL-P (total)	35.7 µmol/L		34.9	30.5	26.7	

		low	25th	50th	75th	high
SMALL LDL-P	583 nmol/L		117	527	839	

		23.0	Large (Pattern A)	20.6	20.5	Small (Pattern B)	19.0
LDL SIZE	21.5 nm						

Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account.

LipoProtein Markers Associated with Insulin Resistance & Diabetes Risk②③ — Insulin Sensitive ← Percentile in Reference Population① → Insulin Resistant

		low	25th	50th	75th	high
LARGE VLDL-P	<0.8 nmol/L		0.9	2.7	6.9	
SMALL LDL-P	583 nmol/L		117	527	839	

		high	75th	50th	25th	low
LARGE HDL-P	9.9 µmol/L		7.3	4.8	3.1	

		small	25th	50th	75th	large
VLDL SIZE	33.5 nm		42.4	46.6	52.5	

		large	75th	50th	25th	small
LDL SIZE	21.5 nm		21.2	20.8	20.4	
HDL SIZE	9.4 nm	large	9.6	9.2	8.9	small

Insulin Resistance Score

		insulin sensitive	25th	50th	75th	insulin resistant
LP-IR SCORE**	0-100 <25		27	45	63	

** The LP-IR score is a laboratory developed index that has been associated with insulin resistance and diabetes risk and should be used as one component of a physician's clinical assessment. Neither the LP-IR score nor the subclasses listed above have been cleared by the US Food and Drug Administration.

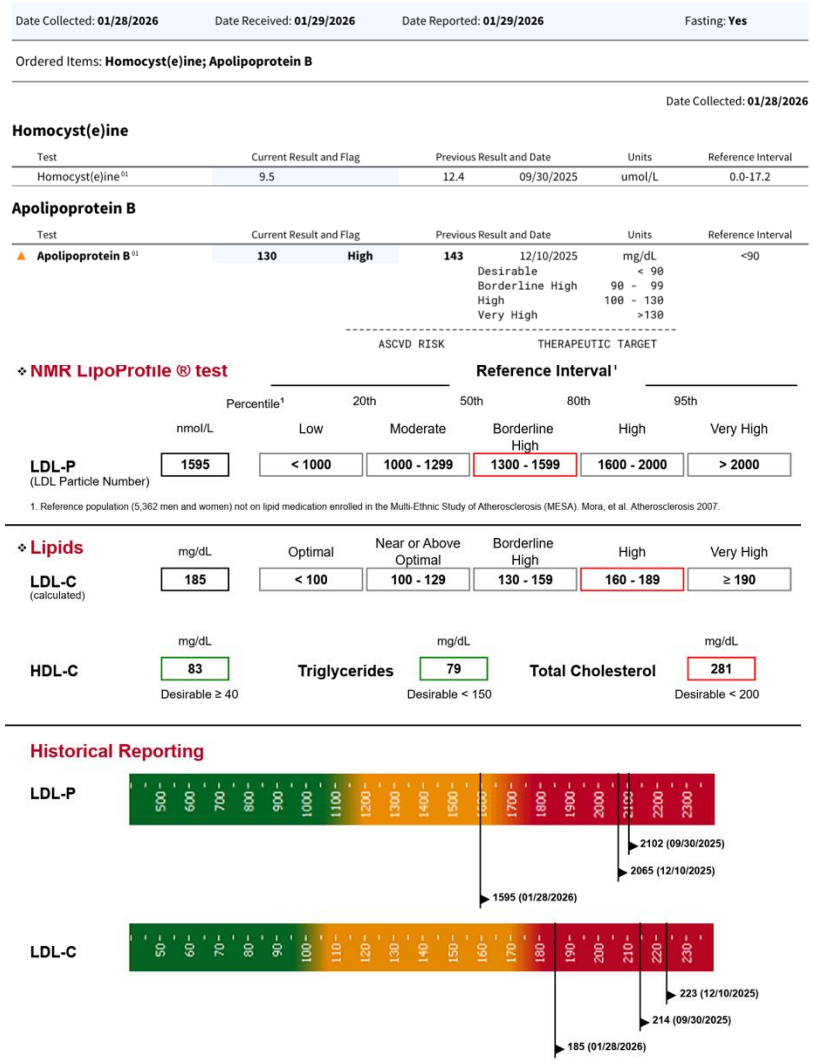
This test was developed and its performance characteristics determined by LabCorp. It has not been cleared or approved by the US Food and Drug

Leading up to this blood draw, patient has been on several nutrients months prior-

- Red Yeast Rice
- Omega 3
- Multi-vitamin
- Electrolytes

Patient was switched to: Combination Cardio Specific Product 2 b.i.d.

6-Week Follow Up Bloodwork



Date Collected: **01/28/2026** Date Received: **01/29/2026** Date Reported: **01/29/2026** Fasting: **Yes**

Ordered Items: **Homocyst(e)ine; Apolipoprotein B**

Date Collected: **01/28/2026**

Homocyst(e)ine

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Homocyst(e)ine[01]	9.5	12.4 09/30/2025	umol/L	0.0-17.2

Apolipoprotein B

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ Apolipoprotein B[01]	130 High	143 12/10/2025	mg/dL	<90

Desirable < 90
Borderline High 90 - 99
High 100 - 130
Very High >130

ASCVD RISK THERAPEUTIC TARGET

NMR LipoProfile ® test — Reference Interval[1]

	nmol/L	Percentile[1] Low	20th Moderate	50th Borderline High	80th High	95th Very High
LDL-P (LDL Particle Number)	1595	< 1000	1000 - 1299	1300 - 1599	1600 - 2000	> 2000

1. Reference population (5,362 men and women) not on lipid medication enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA). Mora, et al. Atherosclerosis 2007.

Lipids

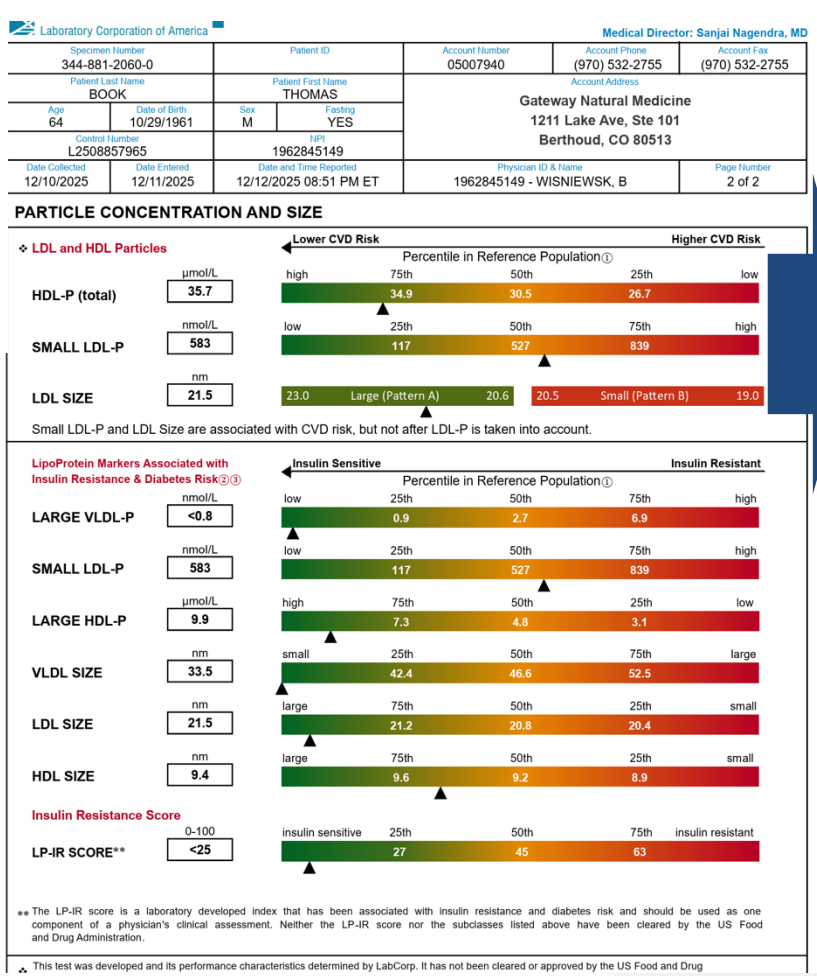
	mg/dL	Optimal	Near or Above Optimal	Borderline High	High	Very High
LDL-C (calculated)	185	< 100	100 - 129	130 - 159	160 - 189	≥ 190

HDL-C	Triglycerides	Total Cholesterol
83 mg/dL	79 mg/dL	281 mg/dL
Desirable ≥ 40	Desirable < 150	Desirable < 200

Historical Reporting

LDL-P

LDL-C



Laboratory Corporation of America — Medical Director: Sanjai Nagendra, MD

Specimen Number	Patient ID	Account Number	Account Phone	Account Fax
344-881-2060-0		05007940	(970) 532-2755	(970) 532-2755

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Age	Date of Birth	Sex	Fasting
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Control Number	NPI
L2508857965	1962845149

Date Collected	Date Entered	Date and Time Reported	Physician ID & Name	Page Number
12/10/2025	12/11/2025	12/12/2025 08:51 PM ET	1962845149 - WISNIEWSK, B	2 of 2

PARTICLE CONCENTRATION AND SIZE

LDL and HDL Particles — Lower CVD Risk / Higher CVD Risk; Percentile in Reference Population

		high	75th	50th	25th	low
HDL-P (total)	35.7 µmol/L		34.9	30.5	26.7	

		low	25th	50th	75th	high
SMALL LDL-P	583 nmol/L		117	527	839	

LDL SIZE	21.5 nm	23.0 Large (Pattern A)	20.6	20.5 Small (Pattern B)	19.0

Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account.

LipoProtein Markers Associated with Insulin Resistance & Diabetes Risk — Insulin Sensitive / Insulin Resistant; Percentile in Reference Population

		low	25th	50th	75th	high
LARGE VLDL-P	<0.8 nmol/L		0.9	2.7	6.9	
SMALL LDL-P	583 nmol/L		117	527	839	

		high	75th	50th	25th	low
LARGE HDL-P	9.9 µmol/L		7.3	4.8	3.1	

		small	25th	50th	75th	large
VLDL SIZE	33.5 nm		42.4	46.6	52.5	

		large	75th	50th	25th	small
LDL SIZE	21.5 nm		21.2	20.8	20.4	

		large	75th	50th	25th	small
HDL SIZE	9.4 nm		9.6	9.2	8.9	

Insulin Resistance Score

		insulin sensitive	25th	50th	75th	insulin resistant
LP-IR SCORE**	0-100 <25		27	45	63	

** The LP-IR score is a laboratory developed index that has been associated with insulin resistance and diabetes risk and should be used as one component of a physician's clinical assessment. Neither the LP-IR score nor the subclasses listed above have been cleared by the US Food and Drug Administration.

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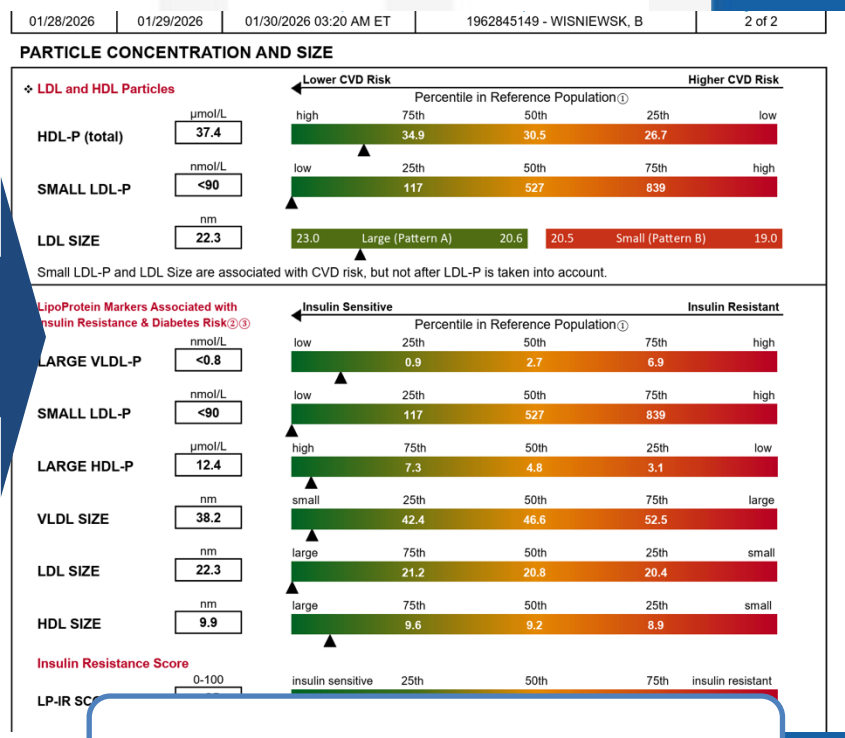


01/28/2026	01/29/2026	01/30/2026 03:20 AM ET	1962845149 - WISNIEWSK, B	2 of 2

PARTICLE CONCENTRATION AND SIZE

LDL and HDL Particles — Lower CVD Risk / Higher CVD Risk; Percentile in Reference Population

		high	75th	50th	25th	low
HDL-P (total)	37.4 µmol/L		34.9	30.5	26.7	

		low	25th	50th	75th	high
SMALL LDL-P	<90 nmol/L		117	527	839	

LDL SIZE	22.3 nm	23.0 Large (Pattern A)	20.6	20.5 Small (Pattern B)	19.0

Small LDL-P and LDL Size are associated with CVD risk, but not after LDL-P is taken into account.

LipoProtein Markers Associated with Insulin Resistance & Diabetes Risk — Insulin Sensitive / Insulin Resistant; Percentile in Reference Population

		low	25th	50th	75th	high
LARGE VLDL-P	<0.8 nmol/L		0.9	2.7	6.9	
SMALL LDL-P	<90 nmol/L		117	527	839	

		high	75th	50th	25th	low
LARGE HDL-P	12.4 µmol/L		7.3	4.8	3.1	

		small	25th	50th	75th	large
VLDL SIZE	38.2 nm		42.4	46.6	52.5	

		large	75th	50th	25th	small
LDL SIZE	22.3 nm		21.2	20.8	20.4	

		large	75th	50th	25th	small
HDL SIZE	9.9 nm		9.6	9.2	8.9	

Insulin Resistance Score

		insulin sensitive	25th	50th	75th	insulin resistant
LP-IR SC	0-100					

At ROF appointment patient mentions only taking 2 **Combination Cardio Specific Product** per day instead of the 4 recommended.

53YO Female – Elevated ox-LDL

Date Collected: **01/27/2026** Date Received: **01/28/2026** Date Reported: **01/30/2026** Fasting: **Yes**

Ordered Items: **Lipid Panel w/ Chol/HDL Ratio; Oxidized LDL; CA 27.29**

Date Collected: **01/27/2026**

Lipid Panel w/ Chol/HDL Ratio

Test	Current Result and Flag		Previous Result and Date		Units	Reference Interval
▲ **Cholesterol, Total** [01]	**210**	**High**	**256**	12/04/2025	mg/dL	100-199
Triglycerides [01]	60		75	12/04/2025	mg/dL	0-149
HDL Cholesterol [01]	66		68	12/04/2025	mg/dL	>39
VLDL Cholesterol Cal	11		12	12/04/2025	mg/dL	5-40
▲ **LDL Chol Calc (NIH)**	**133**	**High**	**176**	12/04/2025	mg/dL	0-99
T. Chol/HDL Ratio	3.2		3.8	12/04/2025	ratio	0.0-4.4
Please Note: [01]						

T. Chol/HDL Ratio

	Men	Women
1/2 Avg.Risk	3.4	3.3
Avg.Risk	5.0	4.4
2X Avg.Risk	9.6	7.1
3X Avg.Risk	23.4	11.0

Oxidized LDL

Test	Current Result and Flag		Previous Result and Date		Units	Reference Interval
▲ **Oxidized LDL** [02]	**1750**	**High**	**>2500**	12/04/2025	ng/mL	10-170

Results verified by repeat testing

CA 27.29

Test	Current Result and Flag	Previous Result and Date		Units	Reference Interval
CA 27.29 [03]	25.9	**39.2**	12/04/2025	U/mL	0.0-38.6

Siemens Centaur Immunochemiluminometric Methodology (ICMA)
Values obtained with different assay methods or kits cannot be used interchangeably. Results cannot be interpreted as absolute evidence of the presence or absence of malignant disease.

Therapeutic Plan

- Combination Cardio Specific Product
- Omega 3 Pro-Resolvins
- Emulsified Vitamin D

Omega-3 Oils Dosage Timing

Compartment	Incorporation Speed (Start of Supplementation)	Time to Meaningful Elevation	Time Toward Steady State	Decline Timeline After Stopping	Mechanistic Reason
Plasma Phospholipids	24–72 hours	3–7 days	~1–2 weeks	Drops within days	Reflects recent intake only
Whole Blood	3–7 days	1–2 weeks	~4 weeks	2–4 weeks	Mix of plasma + RBC pool
RBC Membranes (Omega-3 Index)	1–2 weeks	~4 weeks (~30 days)	8–16 weeks	Gradual decline over 8–16 weeks (≈120 days total)	RBC lifespan ~120 days
Myocardial Tissue	Several weeks	4–8 weeks	8–16 weeks	Weeks to months	Slower membrane remodeling
Brain Tissue	Slow	8–12+ weeks	Months	Months	DHA tightly regulated, slow turnover

Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev Med. 2004;39(1):212-220.
Flock MR, Skulas-Ray AC, Harris WS, Etherton TD, Fleming JA, Kris-Etherton PM. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial. J Am Heart Assoc. 2013;2(6):e000513.
Browning LM, Walker CG, Mander AP, et al. Incorporation of eicosapentaenoic and docosahexaenoic acids into lipid pools when given as supplements providing doses equivalent to typical intakes of oily fish. Am J Clin Nutr. 2012;96(4):748-758. Katan MB, Deslypere JP, van Birgelen APJM, Penders M, Zegwaard M. Kinetics of incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study. J Lipid Res. 1997;38(10):2012-2022.
Metcalf RG, James MJ, Gibson RA, et al. Effects of fish-oil supplementation on myocardial fatty acids in humans. Am J Clin Nutr. 2007;85(5):1222-1228.

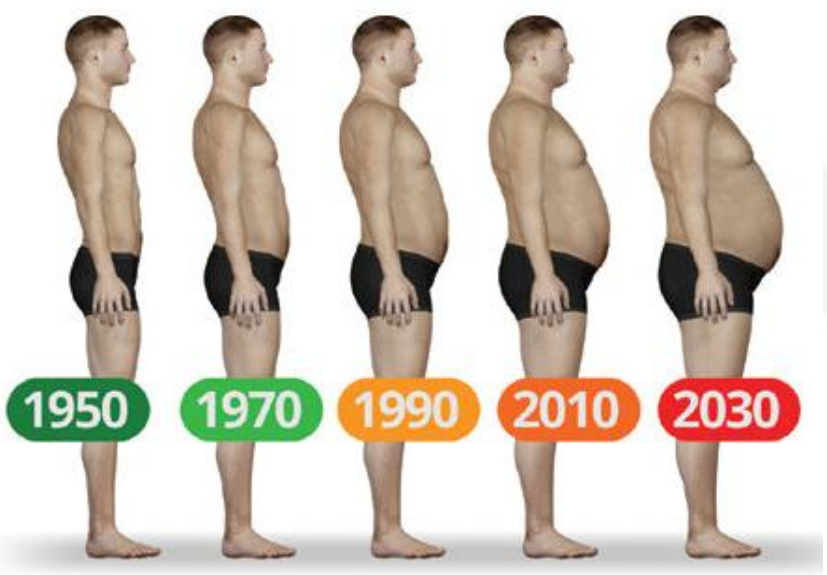
Obesity Epidemic (1980s - Present)

Before 1980: U.S. obesity rates were **relatively low** (approx. 13% of adults).
After Low-Fat Guidelines (1980-Present): Obesity rates skyrocketed:

- 1980: **13% of adults obese**
- 2000: **30% of adults obese**
- 2022: **42% of adults obese** (CDC data)

The shift to **low-fat, high-carb diets** led to:

- Increased processed and refined carbs (bread, pasta, sugar)
- Reduced intake of satiating fats → leading to overeating
- Higher reliance on industrial seed oils (which *may* contribute to inflammation)



Type II Diabetes Explosion

1980: approx. 5.5 million Americans had **type 2 diabetes**.

2020: Over **37 million** Americans now have **diabetes**, with **96 million** more in the **prediabetic range** (how many more may be undiagnosed?).

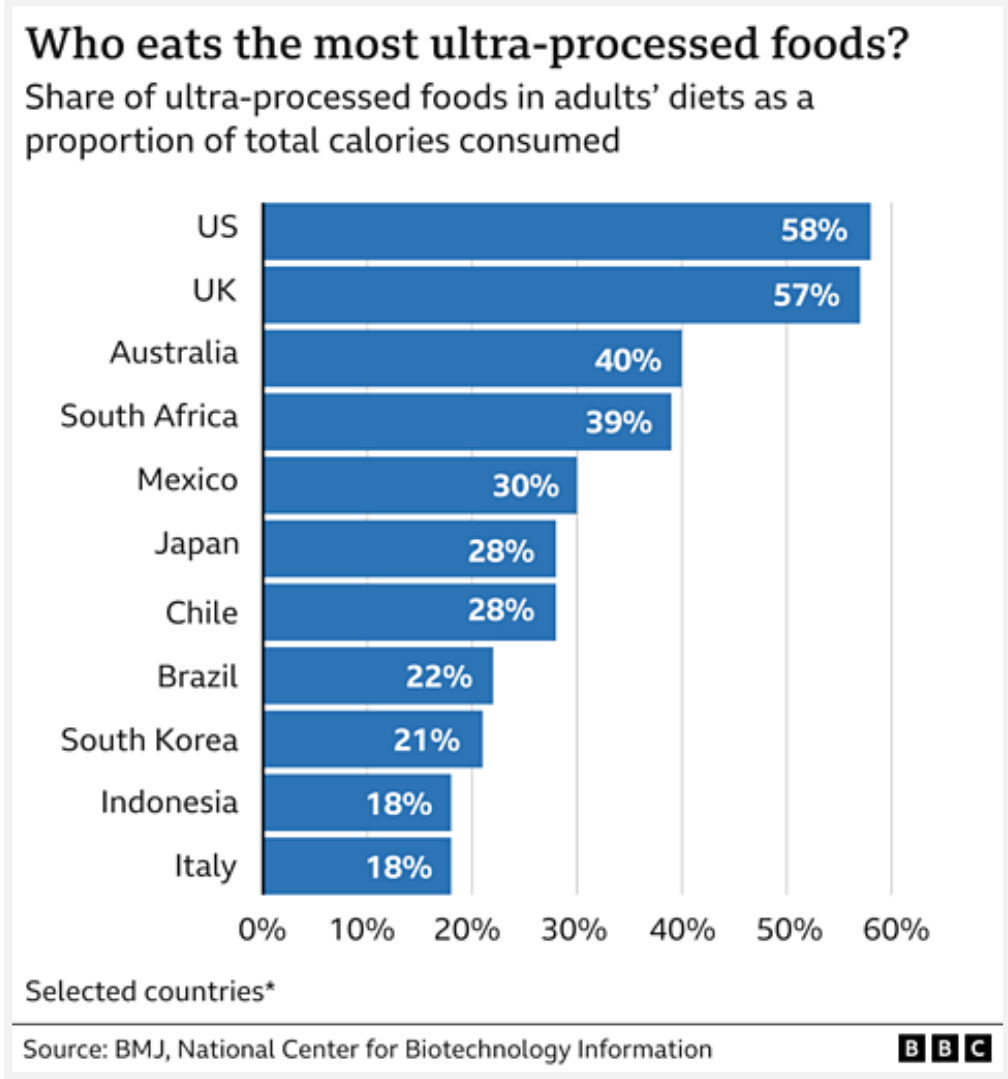
Connection to Diet? The low-fat movement:

- Led to **higher sugar and refined carb intake**, increasing **insulin resistance**.
- Encouraged **frequent eating/snacking**, preventing metabolic flexibility.
- Removed emphasis on **nutrient-dense whole foods**, which regulate blood sugar.

Ultra Processed Food

CDC released a report saying that 55% of the total calories eaten by Americans age 1 or older came from ultra processed food during a 2021–2023 observation period.

- Children (anyone 18 and under) consumed UPFs for 61.9% of all calories.
- Adults age 19 and older got 53% of their calories from UPFs.



https://abcnews.go.com/Health/americans-consume-half-calories-ultra-processed-foods-cdc/story?id=124371719

69YO Male – Type II Diabetes, Hyperlipidemia, Chronic UTI (3yr), Neuropathy

Long term, non-compliant patient whose A1c continues to climb with associated metabolic findings

Patient was ready to start making significant changes summer 2025. He swears he has been eating appropriately and exercising and now he isn't seeing any improvements. He is also starting to have issues with peripheral neuropathy.

Recently Added:

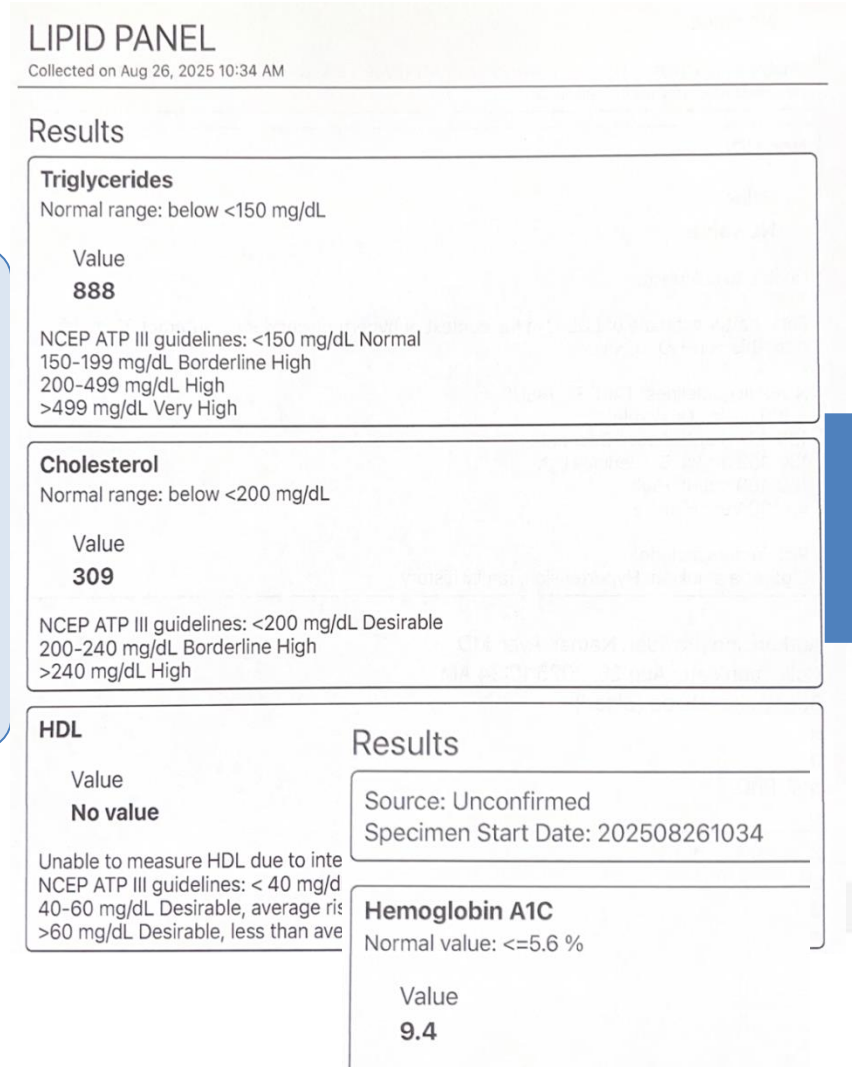
- Jardiance

Carvedilol	Coureg	6.25 mg	1 tablet	2 x daily	CHF
Aspirin		81 mg	1 tablet	1 x daily	
Fenofibrate	Lofibra	160 mg	1 tablet	1 x daily	Hyperlipidemia
Losartan		50 mg	1 tablet	1 x daily	Hypertension
Metformin	Glucophage	1000 mg	1 tablet	2 x daily	For Diabetes
Rosuvastatin		20 mg	1 tablet	1 x daily	Hyperlipidemia
Tedalfil	Cialis	5 mg	1 tablet	1 x daily	Erection Direction
Glucosamine Hydrochloride	MSM	1500 mg	2 Tablets	1 x daily	w/ MSM Methylsulfonylmethane 1500 mg
Cranberry Fruit Extract	Cranberry PO	650 mg	1 capsule	1 x daily	urinary health
Omega 3 Fish Oil	Viva Naturals	2200 mg FIsh OIL	2 Softgels	1 x daily	1400 mg EPA , 400 mg DHA
Zinc	Zinc Glutonate	50mg	1 tablet	1 x daily	
Vitamin C		100 mg	1 tablet	1 x daily	
Vitamin E	di-alpha tocopheryl acetate	180 mg	1 soft gel	1 x daily	
Vitamin D3 + Magnesium	D3 Cholecalciferol	50 mcg 2000iu	1 tablet	1 x daily	Magnesium Citrate
Melatonin 5 mg			2 tablets	nightly	
Qunol COQ10 Liquid		30 ml daily			
Vascular Sirt FullScript			5 capsules	1 x daily	Recommended is 2 x daily

69YO Male – Type II Diabetes, Hyperlipidemia, Chronic UTI (3yr), Neuropathy

Labs from PCP Prior to Appointment (8.2025)

Triglycerides (fasting): 888
Cholesterol: 309
HDL: unable to measure due to triglyceride concentration
HbA1c: 9.4



LIPID PANEL
Collected on Aug 26, 2025 10:34 AM

Results

Triglycerides
Normal range: below <150 mg/dL

Value
888

NCEP ATP III guidelines: <150 mg/dL Normal
150-199 mg/dL Borderline High
200-499 mg/dL High
>499 mg/dL Very High

Cholesterol
Normal range: below <200 mg/dL

Value
309

NCEP ATP III guidelines: <200 mg/dL Desirable
200-240 mg/dL Borderline High
>240 mg/dL High

HDL

Value
No value

Unable to measure HDL due to inte
NCEP ATP III guidelines: < 40 mg/d
40-60 mg/dL Desirable, average ris
>60 mg/dL Desirable, less than ave

Results

Source: Unconfirmed
Specimen Start Date: 202508261034

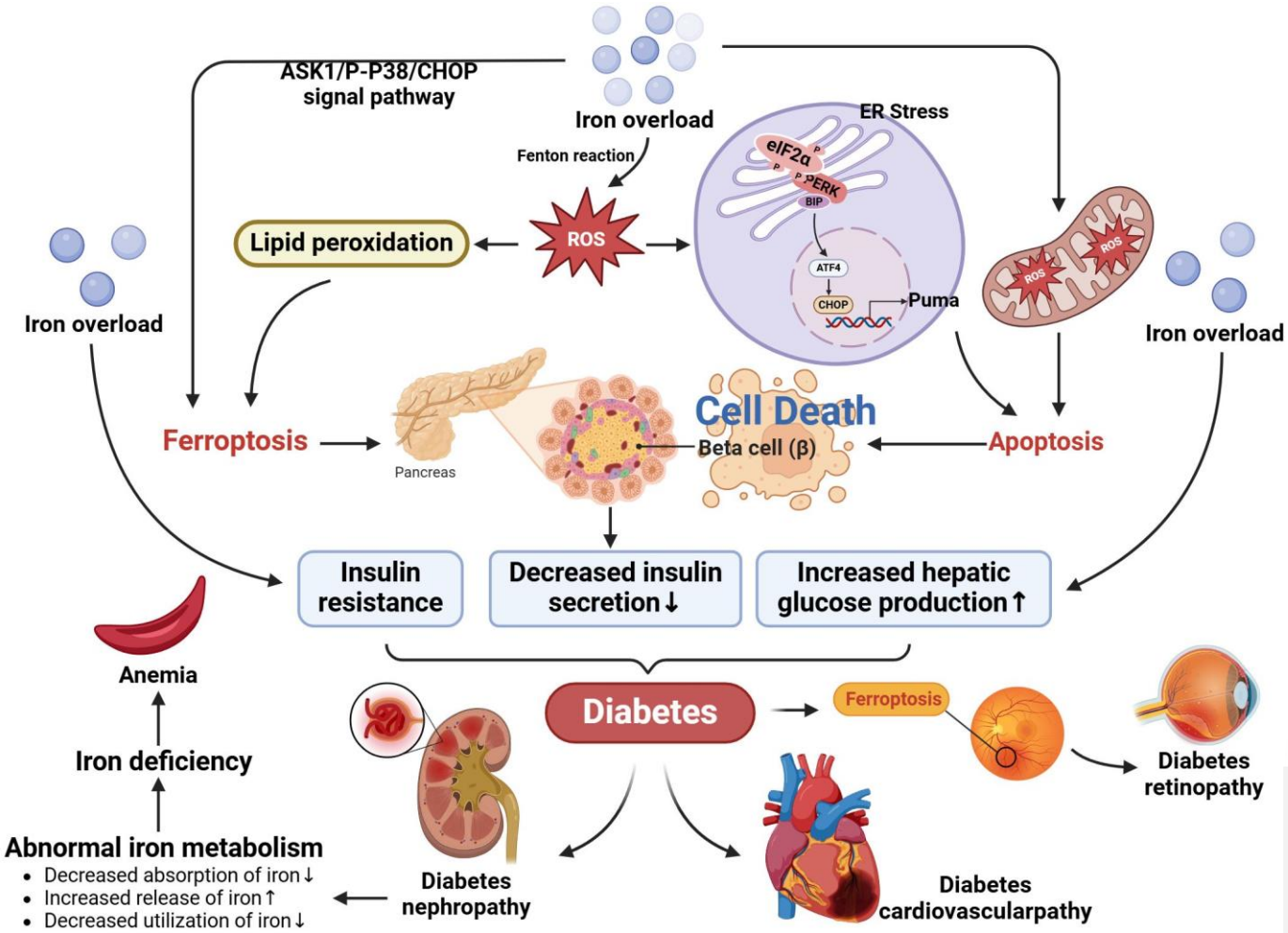
Hemoglobin A1C
Normal value: <=5.6 %

Value
9.4

Plan:
Recommended PCP order HbA1c at appropriate intervals *(He wants to continue to get basic labs through PCP)*

Assess insulin dysfunction – After further questioning the patient it appears he eats a lot of seafood, specifically sardines- curious about heavy metal influence

Insulin Dysfunction Due To Metal Ion Interaction



Arsenic → impairs mitochondrial respiration + alters PDH → ROS via ETC disruption

Mercury → binds sulfhydryl groups → depletes glutathione → indirect ROS rise

Lead → disrupts antioxidant enzymes (SOD, catalase) + calcium signaling

Figure 1. Metal ion metabolism. The main components involved in metal ion metabolism and homeostatic regulation include transporters, metal-blinding chaperones, and metalloproteins.

69YO Male – Type II Diabetes, Hyperlipidemia, Chronic UTI (3yr), Neuropathy

Date Collected: **09/04/2025** Date Received: **09/05/2025** Date Reported: **09/05/2025** Fasting: **Yes**

Ordered Items: **Urinalysis, Complete; C-Reactive Protein, Cardiac; Homocyst(e)ine**

Date Collected: **09/04/2025**

Urinalysis, Complete

Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
Urinalysis Gross Exam [01]					
Specific Gravity [01]	1.014				1.005-1.030
pH [01]	6.5				5.0-7.5
Urine-Color [01]	Yellow				Yellow
Appearance [01]	Clear				Clear
▶ **WBC Esterase** [01]	**3+**	**Abnormal**			Negative
Protein [01]	Negative				Negative/Trace
Glucose [01]	Negative				Negative
Ketones [01]	Negative				Negative
Occult Blood [01]	Negative				Negative
Bilirubin [01]	Negative				Negative
Urobilinogen,Semi-Qn [01]	0.2			mg/dL	0.2-1.0
Nitrite, Urine [01]	Negative				Negative
Microscopic Examination [01]	See below:				
	Microscopic was indicated and was performed.				
▶ **WBC** [01]	**>30**	**Abnormal**		/hpf	0-5
RBC [01]	None seen			/hpf	0-2
Epithelial Cells (non renal) [01]	None seen			/hpf	0-10
Casts [01]	None seen			/lpf	None seen
▶ **Bacteria** [01]	**Moderate**	**Abnormal**			None seen/Few

C-Reactive Protein, Cardiac

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
C-Reactive Protein, Cardiac [01]	0.50		mg/L	0.00-3.00
	Relative Risk for Future Cardiovascular Event			
	Low		<1.00	
	Average		1.00 - 3.00	
	High		>3.00	

Homocyst(e)ine

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Homocyst(e)ine [01]	13.2		umol/L	0.0-17.2

Date Collected: **09/04/2025** Date Received: **09/05/2025** Date Reported: **09/11/2025** Fasting: **Yes**

Ordered Items: **Heavy Metals Profile I, Blood**

Date Collected: **09/04/2025**

Heavy Metals Profile I, Blood

Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
Lead, Blood [A, 01]	<1.0			ug/dL	0.0-3.4
	Blood Lead Collection Method: Venous				
	Testing performed by Inductively coupled plasma/Mass Spectrometry.				
	Environmental Exposure:				
	WHO Recommendation <5.0				
	Occupational Exposure:				
	OSHA Lead Std 40.0				
	BEI 30.0				
	Detection Limit = 1.0				
▲ **Arsenic, Blood** [A, 01]	**12**	**High**		ug/L	0-9
	Detection Limit = 1				
Comment: [01]					
	Physiologic arsenic concentrations in unexposed individuals are usually less than 10 ug/L; however, the total arsenic concentrations may be markedly increased after dietary consumption of seafood. It may be appropriate to follow up on elevated values with an arsenic test in urine, the preferred specimen type, in order to determine if the arsenic is a toxic inorganic species.				
Mercury, Blood [A, 01]	4.7			ug/L	0.0-14.9
	Detection Limit = 1.0				

Establishing a baseline for UTI
Homocysteine: surrogate marker for B-vitamin metabolism and methylation status
High levels of Arsenic and Mercury

69YO Male – Type II Diabetes, Hyperlipidemia, Chronic UTI (3yr), Neuropathy

9.2025 Treatment

- **NAC:** 500mg; 3x per day
- **Berberine HCl**: 1 with each meal (monitor sugar levels)
- **5-MTHF**: ~ 10,000mcg per day
- **Lipoic Acid**: 600mg per day
- **Vitamin B12**: 2-5,000mcg per day
- **High Potency Multivitmain**: 3 b.i.d.
- **Omega-3**: 2,000mg per day
- (He is on basic nutrients D, Mg, Zinc, etc. on his own)

Additional Recommendations
10 min walk after each meal
120min resistive training per week
Clean Keto Handout (less than 40g total carbs per day); no sardines
mHBOT 2-60min sessions per week; 6 sessions
2 Class IV laser treatments per week
Acupuncture 1-2x per week (neuropathy protocol)

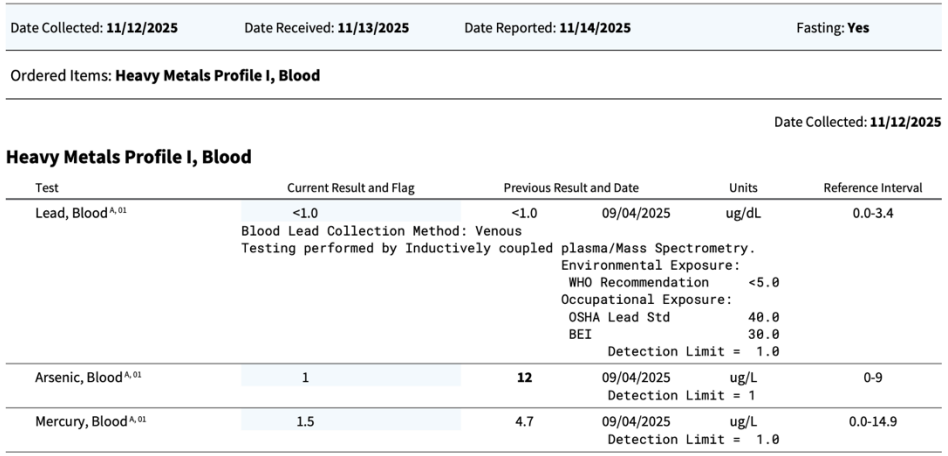
69YO Male – Type II Diabetes, Hyperlipidemia, Chronic UTI (3yr), Neuropathy

Collected on Nov 11, 2025 12:12 PM

Not yet reviewed by care team.

Results

Color Urine Normal value: Yellow Value **Yellow**	**Appearance Urine** Normal value: Clear Value **Clear**
Specific Gravity Urine Normal range: 1.005 - 1.030 1.015 1.005 1.03	**pH Urine** Normal range: 5.0 - 8.0 6 5 8
Protein Urine Normal value: Negative mg/dL Value **Negative**	**Glucose Urine** Normal value: Negative mg/dL Value **Negative**
Ketones Urine Normal value: Negative mg/dL Value **Negative**	**Bilirubin Urine** Normal value: Negative Value **Negative**
Blood Urine Normal value: Negative Value **Negative**	**Nitrite Urine** Normal value: Negative Value **Negative**
Urobilinogen Urine Normal value: <2.0 EU/dL Value **0.2**	**Leukocyte Esterase Urine** Normal value: Negative Value **Negative**
White Blood Cells Urine Normal value: <=10 /HPF Value **0-5**	**Red Blood Cells Urine** Normal value: 0 - 2 /HPF Value **0-2**
Bacteria Urine Normal value: Negative /HPF Value **Negative**	**Squamous Epithelial Cells** Normal value: <=10 /HPF Value **0-2**



Date Collected: **11/12/2025** Date Received: **11/13/2025** Date Reported: **11/14/2025** Fasting: **Yes**

Ordered Items: **Heavy Metals Profile I, Blood**

Date Collected: **11/12/2025**

Heavy Metals Profile I, Blood

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Lead, Blood[A,01]	<1.0	<1.0 09/04/2025	ug/dL	0.0-3.4
Blood Lead Collection Method: Venous Testing performed by Inductively coupled plasma/Mass Spectrometry. Environmental Exposure: WHO Recommendation <5.0 Occupational Exposure: OSHA Lead Std 40.0 BEI 30.0 Detection Limit = 1.0				
Arsenic, Blood[A,01]	1	**12** 09/04/2025 Detection Limit = 1	ug/L	0-9
Mercury, Blood[A,01]	1.5	4.7 09/04/2025 Detection Limit = 1.0	ug/L	0.0-14.9

Patient has had a UTI for over 3 years

UA Complete 11.2025: Clean UA

Arsenic 12 → 1

Mercury 4.7 → 1.5

Neuropathy is 70% improved

Plan:

Suggested PCP run HbA1c and Lipids in 1 month

Another UA

Schedule FU with this information, early New Year

Email from Patient February 2.13.26

Labs from my PCP; Compared to 8.2025 values:

- **HbA1c:** 9.4 to 5.5
- **Triglycerides:** 888 to 172

I am off Metformin and Jardiance. I will make an appointment soon to discuss next steps.

Laboratory Studies for Assessing the Metabolic Environment

This is not an all-inclusive list rather an addition to comprehensive work-up:

- Fasting Glucose
- HbA1c
- Fructosamine
- Ox-LDL
- Fasting Lipids
- Fasting Insulin
- C-peptide
- Amylase
- Lactate Dehydrogenase
- Organic Acid Testing

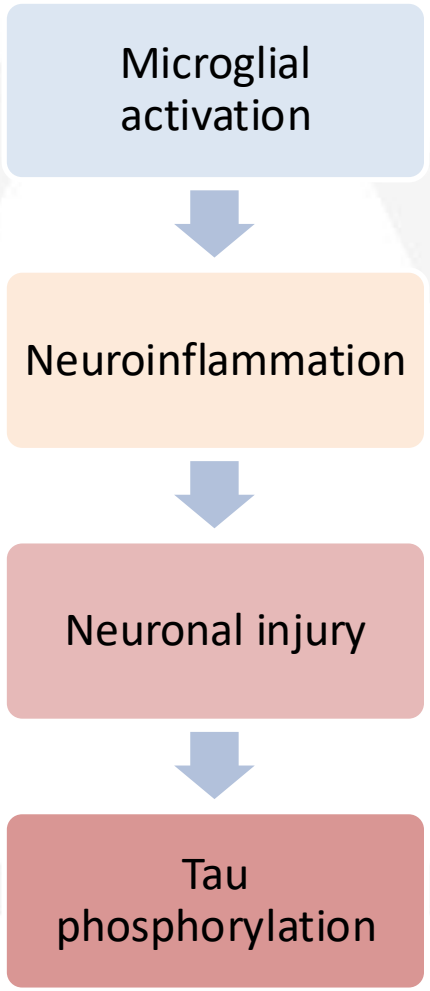
03

CEREBROVASCULAR - NEURODEGENERATION

Blood Brain Barrier Damage

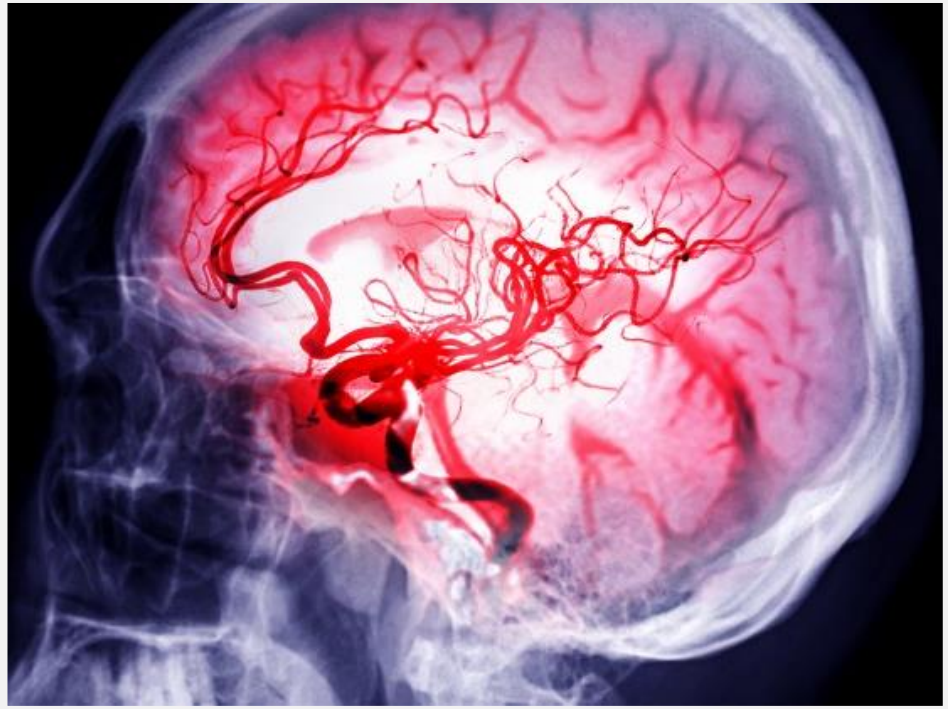
Drivers of BBB Damage

Hypertension
Oxidative lipids (oxLDL)
Chronic inflammation
Hyperglycemia
Homocysteine



Clinical Cerebrovascular Diagnostic Markers

- Lp(a)
- Lp-PLA2
- Oxidized-LDL
- ATN Panel
- Homocysteine
- Insulin
- hs-CRP
- ApoE
- Ferritin
- 8-OHdG (8-hydroxy-2’-deoxyguanosine)



Inflammation and Oxidative Load

Oxidative stress is a physiological state in which systemic levels of reactive oxygen species (ROS) overwhelms the cellular antioxidant buffering capacity, eventually resulting in damage to cellular macromolecules

- Inflammation is part of the immune response, and necessary for life. It's the PRIMARY mechanism of defense against pathogens and an integral part to cellular repair.

High levels or low level chronic inflammatory responses may lead to elevations in **DAMPs** and **antioxidant** depletion a combination referred to **"Inflammaging"**

- This imbalance can be accelerated with things such as radiation, toxic compounds, autoimmune and chronic diseases, obesity, consumption of alcohol, tobacco use….

J Am Diet Assoc. 1996 Jul; 96(7):693-702; quiz 703-4.

Inflammaging: Fenton Reaction

Hydrogen peroxide (H_2O_2) reacts with **ferrous iron** (Fe^{2+}) to generate the **hydroxyl radical (•OH)**, one of the most reactive and damaging free radicals in biology.

Hydroxyl radicals cause **DNA strand breaks, lipid peroxidation, and protein oxidation** almost instantly at their site of generation.

mtDNA has poor repair mechanisms → frequent mutations

Impairs energy production, increase ROS production and leakage

Cell Death | **Expansion of Dysfunctional Cells** | **Immunosenescent Cells**

Inflammaging

Low Grade, Chronic Inflammation

Serum Ferritin

Reflection of brain iron deposition and oxidative stress potential

High serum ferritin may reflect systemic iron overload that parallels iron deposition in the basal ganglia and substantia nigra, contributing to oxidative stress and neurodegenerative processes.

- Higher ferritin levels predicted **faster cognitive decline**.
- Patients with higher ferritin showed **more rapid hippocampal atrophy**.
- Ferritin was strongly associated with CSF apolipoprotein E levels and was elevated by the Alzheimer's risk allele, APOE-ε4 *Nat Commun. 2015 May 19;6:6760. doi: 10.1038/ncomms7760*

Magn Reson Imaging. 1994;12(6):857-867
J Neurol Sci. 2014;345(1-2):123-127
NeuroImage Clin. 2013;3:373-382.

Adjusting Iron Availability

Low iron diets pose risks to other nutrients either due to the dietary co-existence of these compounds or iron being part of the absorption and utilization.

Calcium: (300-600mg with meals) competes in the gut for absorption
Curcumin: acts as an iron chelator- take with iron containing food
Lipoic Acid: (300-600mg on empty stomach) chelates iron and other metals such as copper
Zinc and **Manganese:** (with food) compete with DMT1 transport for absorption
EGCG: inhibits iron absorption

Iron and Oxidation

12-23-2025

30yo F- has been taking iron as part of her pre-pregnancy planning.
Presented to our clinic for a general work-up.

Iron and TIBC

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Iron Bind.Cap.(TIBC)	319			ug/dL	250-450
▼	**UIBC** [01]	**115**	**Low**		ug/dL	131-425
▲	**Iron** [01]	**204**	**High**		ug/dL	27-159
▲	**Iron Saturation**	**64**	**High**		%	15-55

Oxidized LDL

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Oxidized LDL** [02]	**197**	**High**		ng/mL	10-170

Ferritin

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Ferritin [01]	32			ng/mL	15-150

Date Collected: **02/16/2026** Date Received: **02/16/2026** Date Reported: **02/18/2026** Fasting: **Yes**

Ordered Items: **Iron and TIBC; Oxidized LDL; Ferritin; Venipuncture; Lenoir City,TN**

Date Collected: **02/16/2026**

Iron and TIBC

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Iron Bind.Cap.(TIBC)	349		ug/dL	250-450
UIBC [01]	213		ug/dL	131-425
Iron [01]	136		ug/dL	27-159
Iron Saturation	39		%	15-55

Oxidized LDL

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Oxidized LDL [02]	77		ng/mL	10-170

Ferritin

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Ferritin [01]	42		ng/mL	15-150

Treatment: Remove daily iron supplementation

2-16-26:

- ox-LDL: 197 → 77
- Iron: 204 → 136
- Ferritin: 32 → 42

Neurodegeneration (ATN)

Amyloid-β

Aβ42 aggregates extracellularly, forming plaques between neurons.

- **Aβ40** – most common but less toxic
- **Aβ42** – more aggregation-prone and neurotoxic

Accumulation begins **10–20 years before symptoms**

Note: Poor correlation with symptom severity

Tau Phosphorylation

Tau tangles accumulate intracellularly → Neurofibrillary tangles

p-Tau181, p-Tau217

Note: Tau pathology correlates much more closely with cognitive decline than amyloid

Neurofilament Light Chain (NfL)

NfL levels reflect neuronal damage

Sensitive for neuronal damage 80-90%
Specificity for AD 60-70%

Note: Appears in later disease states

Amyloid-Tau-Neurodegeneration (ATN) Profile

Finding	Interpretation	Probably of AD Pathology
A– T– N–	Normal brain aging	--
A+ T– N–	Preclinical Alzheimer's	50-70%
A+ T+ N–	Early Alzheimer pathology	85-90%
A+ T+ N+	Alzheimer disease	90-97%
A– T+ N+	Non-Alzheimer tauopathy	--

74yo Male

Homocyst(e)ine

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Homocyst(e)ine [01]	16.4		umol/L	0.0-19.2

Insulin

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Insulin [01]	3.2		uIU/mL	2.6-24.9

Ferritin

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Ferritin [01]	332		ng/mL	30-400

Date Collected: **03/04/2026**

ATN Profile

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
A -- Beta-amyloid 42/40 Ratio [01]	0.104			>0.102
Beta-amyloid 42 [01]	16.93		pg/mL	
Beta-amyloid 40 [01]	163.06		pg/mL	
▲ **T -- p-tau181** [01]	**1.75** **High**		pg/mL	0.00-0.97
N -- NfL, Plasma [01]	2.05		pg/mL	0.00-6.04
ATN SUMMARY[1]				

Date Collected: **03/02/2026**

APOE Alzheimer's Disease Risk

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
APOE Genotyping Result: [A, 01]	E3/E4 This individual has the APOE E3/E4 genotype. This result is positive for APOE E4, which is associated with increased risk for late-onset Alzheimer's disease. Results should be interpreted in clinical context.			

Amyloid-Tau-Neurodegeneration (ATN) Profile

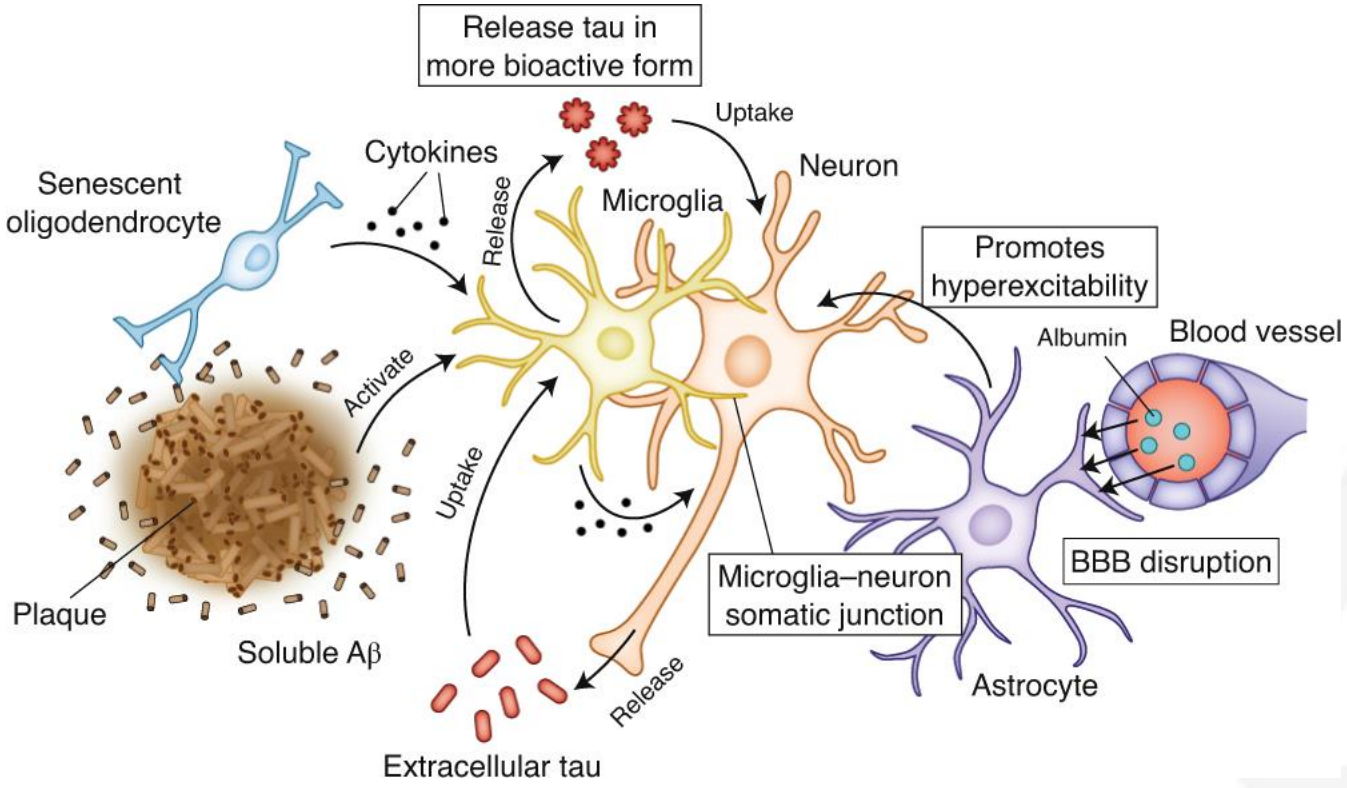
ATN Profile

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▼	**A -- Beta-amyloid 42/40 Ratio** [02]	**0.098**	**Low**			>0.102
	Beta-amyloid 42 [02]	17.06			pg/mL	
	Beta-amyloid 40 [02]	174.67			pg/mL	
▲	**T -- p-tau181** [02]	**1.34**	**High**		pg/mL	0.00-0.97
	N -- NfL, Plasma [02]	2.84			pg/mL	0.00-3.65
	ATN SUMMARY[1]					

A+ T+ N-

A low beta-amyloid 42/40 and a high pTau181 concentration were observed. A normal NfL concentration was observed at this time. These results are consistent with the presence of Alzheimer's related pathology. Plasma findings may be less precise than CSF or PET. Additional assessments may be necessary. These tests are intended to be used in the context of clinical care.

Clinical Diagnostic Workflow



Cognitive testing

MRI brain

Blood biomarkers (ATN Profile) (Aβ42/40, p-tau217, NFL)

If abnormal → PET or CSF confirmation

Vascular Oxidation → Neurodegeneration

Atherogenic Lipids/Oxidation

Lp-PLA2 activation

Lipid inflammatory mediators

Endothelial dysfunction

Blood-brain barrier damage

Microglial activation

GSK-3β activation

Tau phosphorylation → Amyloid Pathology

Neurodegeneration

Common Clinical Biomarkers

- ✓ Lp(a)
- ✓ Lp-PLA2
- ✓ Oxidized-LDL
- ✓ 8-OHdG (8-hydroxy-2'-deoxyguanosine)

AD patients show **30–50% higher ox-LDL levels** compared to controls.

Elevated **Lp-PLA2 increased dementia risk by ~56%**

Plasma Aβ1–40 and Aβ1–42 and the risk of dementia: a prospective case-cohort study. van Oijen, Marieke et al. The Lancet Neurology, Volume 5, Issue 8, 655 - 660

Summary of Testing Methodology

Method	Detects	Accuracy vs pathology	Clinical role
Amyloid PET	Amyloid plaques	~95%	Gold standard for amyloid
Tau PET	Neurofibrillary tangles	~90–95%	Gold standard for tau
CSF biomarkers	Amyloid + tau	~90–95%	Gold standard biochemical
FDG PET	Neuronal metabolism	~85–90%	Functional imaging
MRI	Structural atrophy	~70–85%	Rule-out and staging
Blood biomarkers	Amyloid + tau	~85–95%	Emerging screening tool

Lithium: A Missing Neuroprotective - Signal in Alzheimer's Disease

Lithium deficiency and the onset of Alzheimer's disease

https://doi.org/10.1038/s41586-025-09335-x

Received: 4 September 2024

Accepted: 30 June 2025

Published online: 6 August 2025

Open access

Check for updates

Liviu Aron[1], Zhen Kai Ngian[1], Chenxi Qiu[1], Jaejoon Choi[1], Marianna Liang[1], Derek M. Drake[1], Sara E. Hamplova[1], Ella K. Lacey[1], Perle Roche[1], Monlan Yuan[1], Saba S. Hazaveh[1], Eunjung A. Lee[2], David A. Bennett[3] & Bruce A. Yankner[1]✉

The earliest molecular changes in Alzheimer's disease (AD) are poorly understood[1–5]. Here we show that endogenous lithium (Li) is dynamically regulated in the brain and contributes to cognitive preservation during ageing. Of the metals we analysed, Li was the only one that was significantly reduced in the brain in individuals with mild cognitive impairment (MCI), a precursor to AD. Li bioavailability was further reduced in AD by amyloid sequestration. We explored the role of endogenous Li in the brain by depleting it from the diet of wild-type and AD mouse models. Reducing endogenous cortical Li by approximately 50% markedly increased the deposition of amyloid-β and the accumulation of phospho-tau, and led to pro-inflammatory microglial activation, the loss of synapses, axons and myelin, and accelerated cognitive decline. These effects were mediated, at least in part, through activation of the kinase GSK3β. Single-nucleus RNA-seq showed that Li deficiency gives rise to transcriptome changes in multiple brain cell types that overlap with transcriptome changes in AD. Replacement therapy with lithium orotate, which is a Li salt with reduced amyloid binding, prevents pathological changes and memory loss in AD mouse models and ageing wild-type mice. These findings reveal physiological effects of endogenous Li in the brain and indicate that disruption of Li homeostasis may be an early event in the pathogenesis of AD. Li replacement with amyloid-evading salts is a potential approach to the prevention and treatment of AD.

Lithium levels fall

GSK-3β increases

Amyloid forms

Amyloid binds lithium

Free lithium decreases further

Neurodegeneration accelerates

Aron, L., Ngian, Z.K., Qiu, C. *et al.* Lithium deficiency and the onset of Alzheimer's disease. *Nature* **645**, 712–721 (2025). https://doi.org/10.1038/s41586-025-09335-x

Lithium: A Missing Neuroprotective - Signal in Alzheimer's Disease

Lithium deficiency and the onset of Alzheimer's disease

https://doi.org/10.1038/s41586-025-09335-x
Received: 4 September 2024
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Check for updates

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Restoring lithium prevented neurodegeneration in animal models

<u>In mouse models:</u>

~50% reduction in cortical lithium caused:

- Amyloid-β plaques binds lithium
- Increased phosphorylated tau
- Microglial activation and neuroinflammation
- Loss of synapses, axons, and myelin
- Accelerated cognitive decline

Elemental Lithium: 300-900mcg/day
Lithium Orotate: 5-20mg

Neurodegenerative Timeline

10–20 yrs before symptoms

↑ oxidative lipids

↑ inflammation

↓ vascular function

10 yrs before symptoms

BBB breakdown

Microglial activation

5–10 yrs before symptoms

Amyloid accumulation + Tau phosphorylation

Synaptic loss

Symptoms begin → Cognitive impairment

04 HORMONES

Ideal Hormone Evaluation

- How much is circulating?
- How much is bioavailable at tissue level over time?
- How is it being metabolized and cleared?

“Normal labs but feels terrible”

Serum → normal
Saliva → low free hormone
Urinary → shows high clearance

→ Tissue deficiency despite normal blood level.

Saliva

Free (unbound) hormone fraction
Diurnal cortisol rhythm (AM rise, noon, PM, bedtime)
Tissue-level exposure trends

Urine

Estrogen metabolites (2-OH, 4-OH, 16-OH pathways)
Methylation status
Androgen metabolites
Cortisol metabolites (THF, THE)
Phase I and II detox trends

Serum (Blood) Hormone Testing

What it measures:

- Total and sometimes free hormone levels circulating in the bloodstream.

What's It's Best:

- Best for IM injections, oral hormones (troche, liquid, dry), topicals or pellets

Limitations:

- Can be expensive if ordered correctly. Most doctors only order total/bound hormones.

Saliva Hormone Testing

What it measures:

- The **free, active (unbound)** fraction of hormones that have diffused into tissues and saliva.
- Reflects **real-time bioavailable levels** and **circadian rhythm** (for cortisol, DHEA, etc.).

When it's best:

- Assessing daily hormonal rhythms, i.e. cortisol curve: morning → night
- Tracking menstrual cycle changes or symptoms related to fluctuating free hormone levels.
- Topical (transdermal) hormones — since these may elevate tissue/free levels even when blood tests look normal.
- Tablet or capsulated oral hormones

Limitations:

Cautious of topicals applied to neck and face such as anti-aging creams

Troche or liquid hormones will *soak* the salivary glands falsely elevate levels on test results

Can be easily contaminated (patients must follow directions closely)

64YO Female: Re-eval Appointment

Patient was feeling good and discontinued care. Recently symptoms have started to return so we ordered a follow-up hormone evaluation to start.

Gender	Last Menses	Height	Waist
Female	Unspecified	Unspecified	Unspecified
DOB	**Menses Status**	**Weight**	
3/23/1961 (63 yrs)	Postmenopausal	Unspecified	

TEST NAME	RESULTS | 04/12/24	RANGE
Salivary Steroids & Other Analytes (LC-MS/MS)		
Estradiol	0.4	0.3-0.9 pg/mL Postmenopausal
Estriol	<0.9	<1.9 pg/mL Postmeno or Premeno-Follicular or Synthetic HRT
Estrone	0.9	0.9-3.1 pg/mL Postmeno Premeno-Follicular or Synthetic HRT
Progesterone	<5 L	5-34 pg/mL Postmenopausal
Ratio: Pg/E2 (Saliva LCMS)	N/A	23-196
Testosterone	9	7-22 pg/mL
DHEAS	1.5	0.8-8.0 ng/mL
Cortisol	3.3	2.5-6.2 ng/mL Morning

<dl = Less than the detectable limit of the lab. N/A = Not applicable; 1 or more values used in this calculation is less than the detectable limit. H = High. L = Low.

Therapies

None

Gender	Last Menses	Height	Waist
Female	Unspecified	5 ft 5 in	26 in
DOB	**Menses Status**	**Weight**	**BMI**
3/23/1961 (64 yrs)	Postmenopausal	116 lb	19.3

TEST NAME	RESULTS | 01/10/26	RANGE
Salivary Steroids & Other Analytes (LC-MS/ECLIA)		
Estradiol	325.5 H	0.3-0.9 pg/mL Postmenopausal
Estriol	6885.6 H	<1.9 pg/mL Postmeno or Premeno-Follicular or Synthetic HRT
Estrone	54.3 H	0.9-3.1 pg/mL Postmeno Premeno-Follicular or Synthetic HRT
Progesterone	31	5-34 pg/mL Postmenopausal
Ratio: Pg/E2 (Saliva LCMS)	N/A	23-196
Testosterone	7	7-22 pg/mL
DHEAS	8.2 H	0.8-8.0 ng/mL
Cortisol	3.2	2.5-6.2 ng/mL Morning

<dl = Less than the detectable limit of the lab. N/A = Not applicable; 1 or more values used in this calculation is less than the detectable limit. H = High. L = Low.

Therapies

25mg BID oral DHEA (OTC) (28 Hours Last Used)

64YO Female: Salivary Hormone Results

Patient was extensively questioned:

No new traumas, surgeries

No pelvic complaints, spotting nor bleeding

No bloating

No anti-aging creams or new body products

Diet has been cleaner that ever before

….

Gender	Last Menses	Height	Waist
Female	Unspecified	5 ft 5 in	26 in
DOB	**Menses Status**	**Weight**	**BMI**
3/23/1961 (64 yrs)	Postmenopausal	116 lb	19.3

TEST NAME	RESULTS | 01/10/26	RANGE
Salivary Steroids & Other Analytes (LC-MS/ECLIA)		
Estradiol	325.5 H	0.3-0.9 pg/mL Postmenopausal
Estriol	6885.6 H	<1.9 pg/mL Postmeno or Premeno-Follicular or Synthetic HRT
Estrone	54.3 H	0.9-3.1 pg/mL Postmeno Premeno-Follicular or Synthetic HRT
Progesterone	31	5-34 pg/mL Postmenopausal
Ratio: Pg/E2 (Saliva LCMS)	N/A	23-196
Testosterone	7	7-22 pg/mL
DHEAS	8.2 H	0.8-8.0 ng/mL
Cortisol	3.2	2.5-6.2 ng/mL Morning

<dl = Less than the detectable limit of the lab. N/A = Not applicable; 1 or more values used in this calculation is less than the detectable limit. H = High. L = Low.

Therapies

25mg BID oral DHEA (OTC) (28 Hours Last Used)

64YO Female: Now What?

- Lab error?
- Cancer?
- Hormone secreting tumor?
- Sexual Partner using topical hormones?

Date Collected: **01/27/2026** Date Received: **01/28/2026** Date Reported: **01/28/2026** Fasting: **Not Given**

Ordered Items: **CEA; Cancer Antigen (CA) 125**

Date Collected: **01/27/2026**

CEA

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
CEA [01]	2.4		ng/mL	0.0-4.7
		Nonsmokers	<3.9	
		Smokers	<5.6	

Roche Diagnostics Electrochemiluminescence Immunoassay (ECLIA)
Values obtained with different assay methods or kits cannot be used interchangeably. Results cannot be interpreted as absolute evidence of the presence or absence of malignant disease.

Cancer Antigen (CA) 125

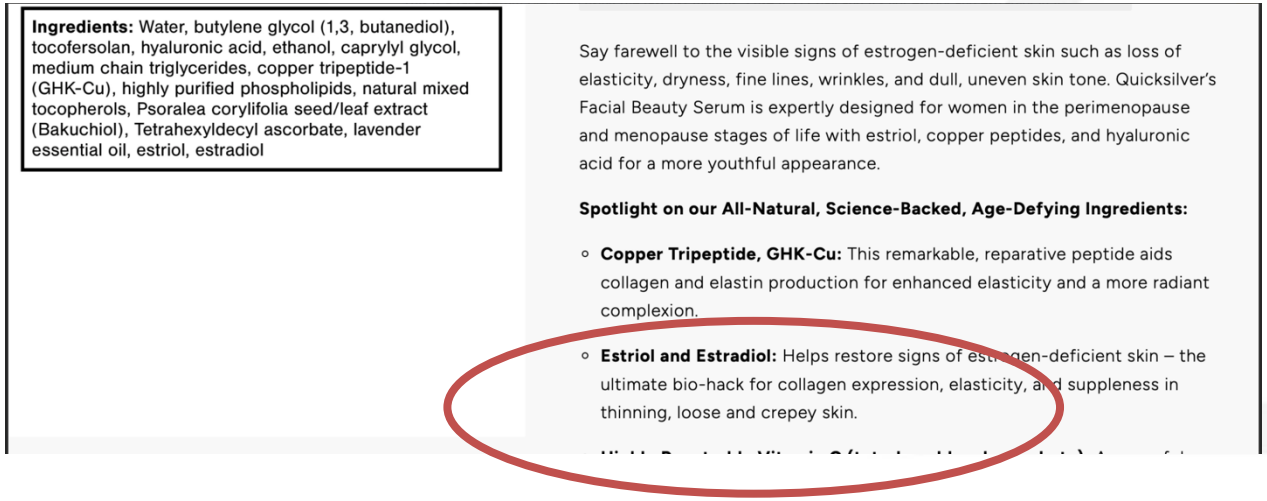
Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Cancer Antigen (CA) 125 [01]	20.9		U/mL	0.0-38.1

Roche Diagnostics Electrochemiluminescence Immunoassay (ECLIA)
Values obtained with different assay methods or kits cannot be used interchangeably. Results cannot be interpreted as absolute evidence of the presence or absence of malignant disease.

Patient was extremely concerned; we decided to start with running a few cancer antigens and suggested serum testing to confirm salivary results.

Email from Patient After Appointment

I may have found the culprit.
This is a face serum I've been using the last 6-7 months. I use it 2/x day and it's got estriol and estradiol in it.



Ingredients: Water, butylene glycol (1,3, butanediol), tocofersolan, hyaluronic acid, ethanol, caprylyl glycol, medium chain triglycerides, copper tripeptide-1 (GHK-Cu), highly purified phospholipids, natural mixed tocopherols, Psoralea corylifolia seed/leaf extract (Bakuchiol), Tetrahexyldecyl ascorbate, lavender essential oil, estriol, estradiol

Say farewell to the visible signs of estrogen-deficient skin such as loss of elasticity, dryness, fine lines, wrinkles, and dull, uneven skin tone. Quicksilver's Facial Beauty Serum is expertly designed for women in the perimenopause and menopause stages of life with estriol, copper peptides, and hyaluronic acid for a more youthful appearance.

Spotlight on our All-Natural, Science-Backed, Age-Defying Ingredients:

- **Copper Tripeptide, GHK-Cu:** This remarkable, reparative peptide aids collagen and elastin production for enhanced elasticity and a more radiant complexion.
- **Estriol and Estradiol:** Helps restore signs of est[illegible]gen-deficient skin – the ultimate bio-hack for collagen expression, elasticity, a[illegible]d suppleness in thinning, loose and crepey skin.

Urine Hormone Testing

What it measures:

- Metabolized hormones → how your body processes and detoxifies them.
- Breakdowns of estrogen (2-OH, 4-OH, 16-OH), androgen, and cortisol pathways.

When it's best:

- For a comprehensive look at hormone metabolism, especially in complex or persistent hormone symptoms.
- For evaluating liver and methylation support needs (Phase I/II detoxification insight).
- Used in alternative oncology to determine the impact certain metabolites can have on mutagenesis

Limitations:

- More complex to interpret.
- Requires accurate timing and collection; hydration can affect results.

Hormone Replacement Therapy (Bioidentical and Synthetic)

After hormonal therapy, to assess **true endogenous production**, you must allow time for:

1. Exogenous hormone clearance
2. Suppressed pituitary signaling (LH/FSH/ACTH) to normalize
3. Downstream gland recovery (testes, ovaries, adrenals)

Hormone Replacement Therapy (Bioidentical and Synthetic)

Oral Hormones: Clear in 1-3 days

- Wait before testing: 6-8 weeks

Topicals: Can accumulate in tissue

- Wait before testing: 4-8 weeks (longer if long term use)

Injectables: can have long half life and likely HPA suppression

- Wait before testing: May not return to baseline for up to 6 months

Pellet: must wait until pellet completely dissipates

- Wait before testing: + 6-8 weeks after pellet is clear

(For Females) In some cases you can monitor cycle – length, flow, symptoms etc. Normally we wait 2-3 full cycles before testing, if possible.

Hormone Replacement Therapy (Bioidentical and Synthetic)

Rank	Delivery Method	Axis Suppression Strength
1	Pellets	🔴 Very High
2	Long-acting injectables	🔴 Very High
3	Oral hormones (esp OCP)	🟠 High
4	Troche / Sublingual	🟠 Moderate–High
5	High-dose transdermal	🟡 Moderate
6	Low-dose transdermal	🟢 Lower
7	Cyclic progesterone	🔵 Minimal

Clinical Pearl:
Dose matters more than route.

Even low-dose estradiol can suppress ovulation in some women.

Long-term use deepens suppression regardless of route.

Hormone Feedback

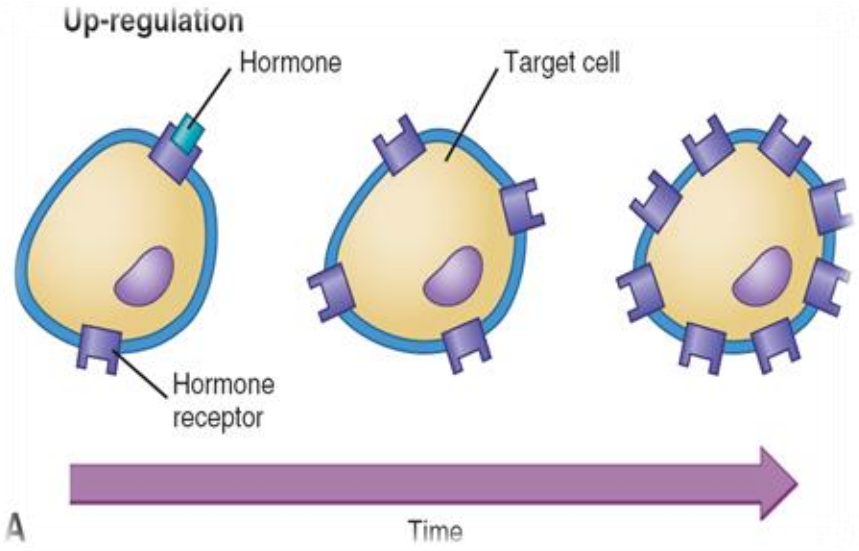
Down-regulation/Negative

- When levels of particular hormone are high, cells become *less* sensitive to it
- The presence of a hormone triggers decrease in number of hormone receptors

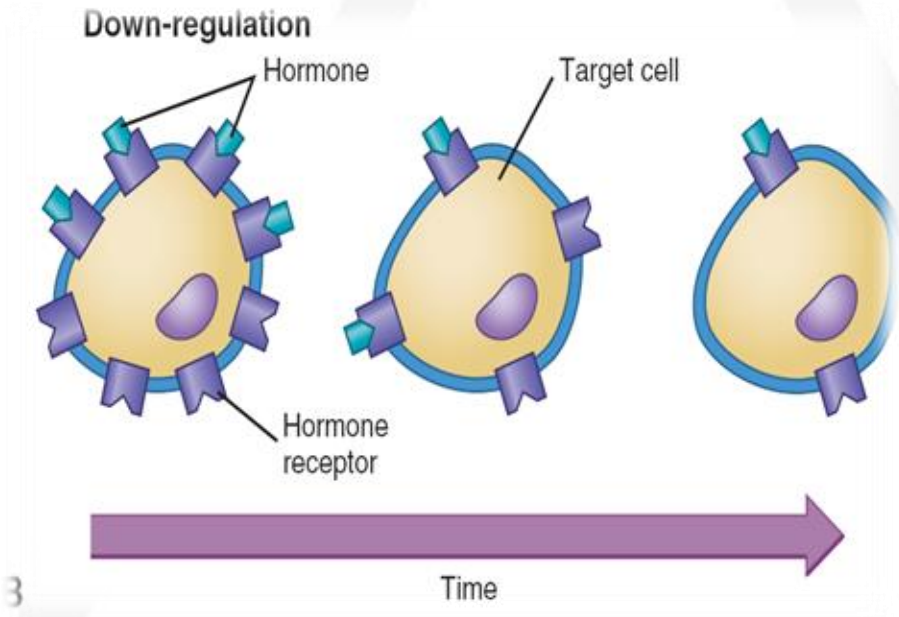
Up-regulation/Positive

- When levels of particular hormone are low, cells become *more* sensitive to it
- Absence of a hormone triggers increase in number of hormone receptors

The Slippery Slope of Replacement



When there is too much hormone the opposite happens and receptors move inwards not allowing binding of a hormone.



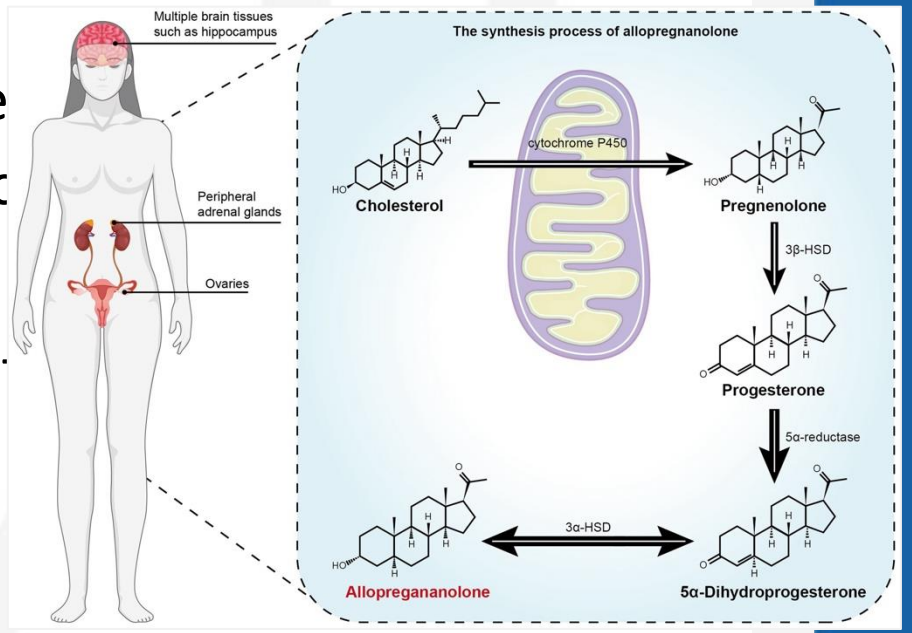
With little available hormone; receptors translocate to the surface to try and “grab” more hormone.

This scenario creates and iatrogenic dependency on administered hormone.
Removing the dose of hormone usual results is a strong negative response in symptoms.
This is much like trying to remove a patient from anti-depressants.

Side Note: Negative Response to Progesterone?

Allopregnanolone (AlloP) is formed from progesterone circulation and directly in the brain. Binds to GABAa rec gabaergic neurons in the brain.

- AlloP has a calming (anxiolytic) and sleep-inducing e



High concentrations: Only high levels of AlloP, achieved at peak of an optimal luteal phase, during pregnancy, and with progesterone therapy, have the anxiolytic effects in the brain.

Low physiological levels: AlloP can have a paradoxical effect, causing anxiety and other symptoms characteristic of premenstrual dysphoric disorder (PMDD).

Side Note: Negative Response to Progesterone?

Weight Gain and Progesterone

Progesterone → **deoxycorticosterone (DOC)**, a mineralocorticoid receptor agonist.

- This can increase sodium reabsorption in the kidney, leading to water retention and bloating (onset: days to a weeks)

- Allopregnanolone → GABA-A receptor modulator → increase appetite
- Suppression of estrogen activity and Progesterone **reduces insulin sensitivity** in skeletal muscle and adipose tissue, partly why insulin resistance naturally rises in pregnancy. (onset: weeks to months)

Try applying hormone vs. by mouth; Add diuretics → Taurine, Vitamin B6, Dandelion

Hormone Transfer

Patient Name: Casey Lauer
Patient Phone Number: 970 396 5960

Gender	Height	Waist
Male	6 ft in	32 in
DOB	**Weight**	**BMI**
2/13/1987 (38 yrs)	190 lb	25.8

TEST NAME	RESULTS | 01/18/26	RANGE
Salivary Steroids & Other Analytes (LC-MS/ECLIA)		
Estradiol	<0.3 L	0.5-1.3 pg/mL
Estriol	3.5 H	<1.7
Estrone	4.2 H	1.3-
Progesterone	28 H	5-2(
Testosterone	60	41-
DHEAS	3.5	0.8-
Cortisol	3.5	2.5-

<dl = Less than the detectable limit of the lab. N/A = Not applicable; 1 or more v

Therapies

None Indicated

38yo Male

Wife is currently on a topical which contains Progesterone (Pg) and Estriol (E3)

Gender	Height	Waist
Male	5 ft 11 in	Unspecified
DOB	**Weight**	**BMI**
5/5/1993 (30 yrs)	190 lb	26.5

TEST NAME	RESULTS | 12/13/23	RANGE
Salivary Steroids		
Estradiol	1.1	0.5-2.2 pg/mL
Progesterone	210 H	12-100 pg/mL
Testosterone	78	44-148 pg/mL (Age Dependent)
DHEAS	11.3	2-23 ng/mL (Age Dependent)

30yo Male

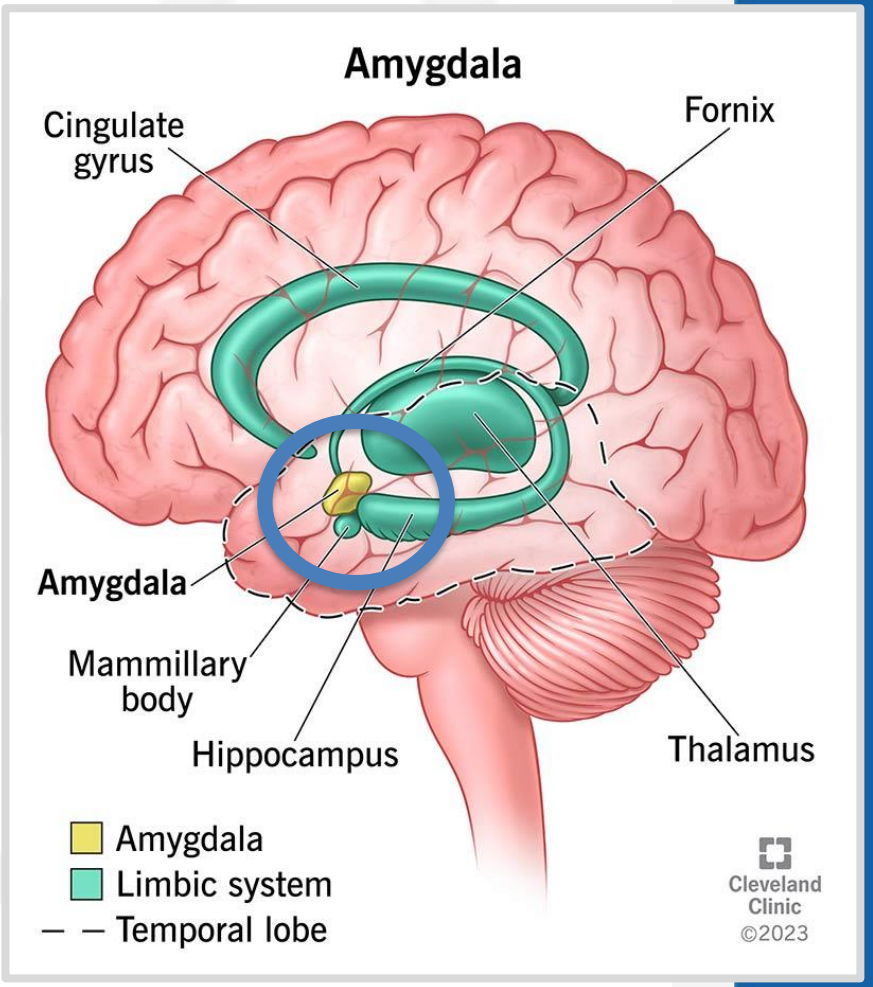
Wife is currently on topical Progesterone (Pg)

Testosterone: Beyond Libido and ED
Amygdala: Heightened Emotional Reactivity

The **amygdala** → regulates fear, stress, and emotional responses, often becomes hyperactive and larger in adults with ELS.

Corticotropin releasing hormone receptor 1 is overexpressed in areas like the amygdala, enhancing the emotional and physiological reactivity to stressors.

- ✓ Overactivation leads to heightened emotional reactivity, increased anxiety, and difficulty regulating stress.
- ✓ Testosterone binds to amygdala and increases the threshold for anxiety



Neuroscience & Biobehavioral Reviews. Volume 27, Issues 1–2, January–March 2003, Pages 33-44

04

HORMONES AND CANCER

Testosterone and Prostate Cancer

Testosterone Therapy and Prostate Cancer Risk

RESEARCH ARTICLE

Testosterone treatment and the risk of aggressive prostate cancer in men with low testosterone levels

Thomas J. Walsh[1,2]*, Molly M. Shores[1,2], Chloe A. Krakauer[2], Christopher W. Forsberg[2], Alexandra E. Fox[2], Kathryn P. Moore[2], Anna Korpak[2], Susan R. Heckbert[1,3], Steven B. Zeliadt[2], Chloe E. Kinsey[2], Mary Lou Thompson[1,2], Nicholas L. Smith[1,2,3], Alvin M. Matsumoto[2,4,5]

1 University of Washington, Seattle, Washington, United States of America, **2** VA Puget Sound Health Care System, Seattle, Washington, United States of America, **3** Group Health Research Institute, Group Health Cooperative, Seattle, Washington, United States of America, **4** Division of Gerontology & Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, Washington, United States of America, **5** Geriatric Research, Education and Clinical Center, VA Puget Sound Health Care System, Seattle, Washington, United States of America

Summary of VA Cohort Study (2002–2012)

Evaluate whether testosterone therapy in men with low testosterone and normal PSA increases the risk of:

- Aggressive prostate cancer (primary outcome)
- Any prostate cancer (secondary outcome)

Study Design and Methods

Cohort of **147,593 men** (ages 40–89) in VA system

- Low testosterone, PSA < 4 ng/mL, no prior prostate/breast cancer
- Within the cohort, 58,617 received testosterone therapy. Three years was the median duration that patients were followed.
  - Testosterone types: IM and topical

Conclusions

The study reported that men who received testosterone therapy were subsequently diagnosed with aggressive prostate cancer at the rate of 0.58 per 1,000 person years. Among untreated men (n = 88,976) the incidence rate was nearly identical: 0.57 per 1,000 person years.

- **Testosterone therapy was not associated with increased risk of prostate cancer**
- **Higher cumulative doses showed lower cancer risk, but not conclusively**

The Saturation Model

Theory as to why some patient's PSA adjust in concordance with testosterone therapy while other's do not:

Androgen Receptor Sensitivity

Anecdotally those patient, with prostate cancer and whose testosterone is low (<250) may see more responsive PSA with testosterone supplementation while those with normal testosterone levels may not

DHT and Prostate Cancer

- **Higher baseline DHT levels** are associated with **improved prostate cancer–specific survival** after diagnosis.
- **Lower DHT levels** appear to correlate with **worse outcomes**, suggesting a protective effect for higher androgen status.

World J Mens Health. 2015 Dec;33(3):125-129. English.
Urology. 2007;70(4):702–705.
Eur Urol. 2007;52(2):322–324.
Endocr Res. 2023;48(4):212–220.

Normal Levels of Testosterone Through Treatment

Benefits	Risks & Monitoring Needs
Improved muscle mass, bone density, and energy in hypogonadal men	**Potential** stimulation of residual or micro-metastatic disease
Enhanced mood, cognition, and libido	Make make tracking PSA levels more difficult
Possible re-differentiation of tumor cells in specific contexts (BAT)	Contraindicated in rapidly progressing or high-grade disease
Improved metabolic profile and reduced ADT-related morbidity	
Increased treatment adherence and quality of life	

PSA Testing

Benign prostatic hyperplasia (BPH):

- More PSA leaks into the blood in the **free/unbound form**.
- %fPSA is **higher**

Prostate cancer:

- PSA is more often secreted bound to serum proteins.
- %fPSA is **lower**

Low %fPSA → higher likelihood of cancer.

High %fPSA → more consistent with BPH.

Clinical tip: Run PSA on your patients early in life *(prostate cancer diagnosed before age of 35 is EXTREMELY RARE)*- establish the patient's baseline
Skene's glands are considered "female prostate"- some breast cancers and PCOS cases can release higher levels of PSA but often too low to reliable interpret.

Non-Invasive Prostate Cancer Testing

Test	Biomarkers / What Is Measured	Sensitivity (GG2+)	Specificity	Main Strength
PSA	Total PSA (kallikrein-related peptidase 3)	60–80%	Low	First-line screening
% Free PSA	Free PSA ÷ Total PSA ratio	65–95%	Low–Mod	Improves gray-zone PSA specificity
PHI	Total PSA, Free PSA, [-2]proPSA	85–90%	30–50%	Better discrimination than PSA alone
4Kscore	Total PSA, Free PSA, Intact PSA, hK2 + clinical variables (age, DRE, prior biopsy)	85–95%	30–60%	Strong risk prediction model
PCA3	PCA3 mRNA (urine after DRE)	60–70%	~70%	Higher specificity than PSA
SelectMDx	HOXC6 mRNA, DLX1 mRNA (urine after DRE)	85–95%	40–50%	High NPV for GG2+
ExoDx (EPI)	Urinary exosomal RNA: ERG, PCA3, SPDEF	~90%	~30–35%	No DRE required; strong rule-out test
mpMRI	Imaging features (T2, DWI/ADC, DCE); PI-RADS scoring	85–95%	65–75%	Best non-invasive structural discriminator

04

HORMONES AND CANCER

Estrogen and Breast Health

Iodine and Breast Tenderness/Fibrocystic Breast

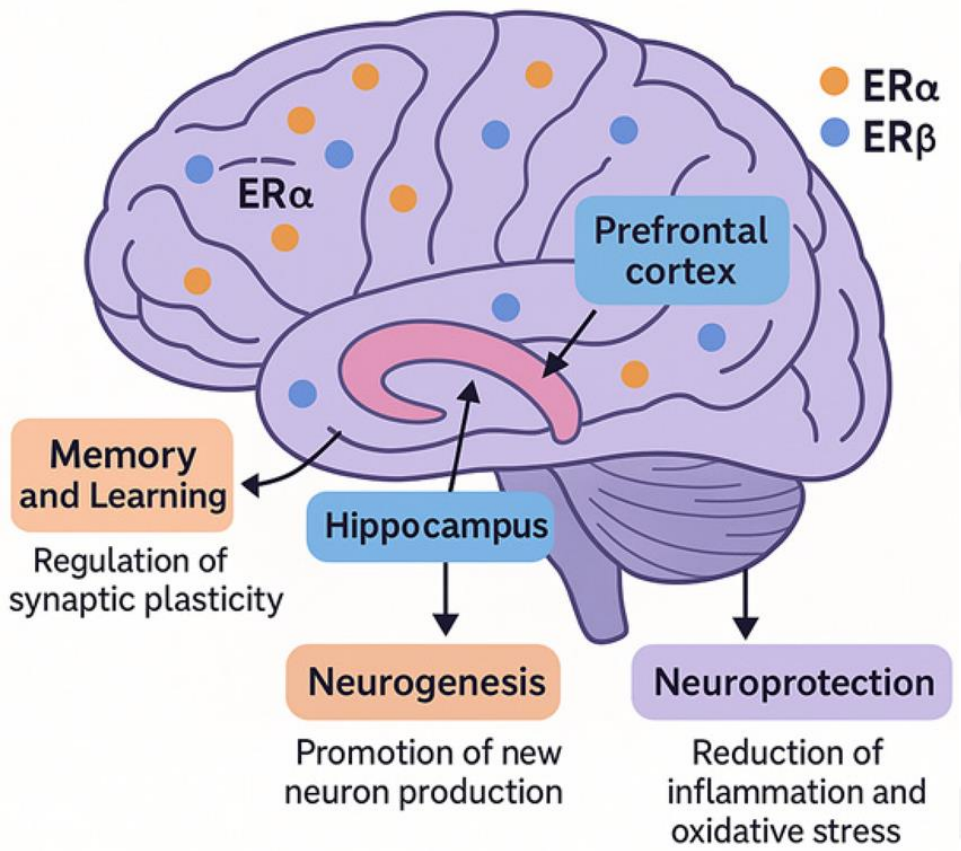
Iodine helps to create an anti-proliferative environment in the breast tissue by the following mechanisms:

- Formation of 6-iodolactone → activates PPAR-γ
- Upregulation of antioxidant enzymes (SOD, catalase, GPx)
- Downregulation of ERα expression
- Modest favorable shifts in estrogen metabolism

Estrogen Receptors (ERα / ERβ)

ERα → proliferative, dominant in breast tissue

ERβ → more modulatory/anti-proliferative



Genistein/Soy Isoflavones

Based on many large studies, eating soy is consistently linked to **lower breast cancer risk** and, in women already diagnosed, **lower recurrence and possibly better survival**—especially in post-menopausal and ER-positive disease.

2022 meta-analyses report a **dose-response reduction in risk** with higher dietary isoflavone intake; one pooled analysis estimated about **~12% lower risk per 10 mg/day** of isoflavones.

The **After Breast Cancer Pooling Project** (n=11,000+) found **≥10 mg/day** post-diagnosis intake was linked to **25% lower recurrence risk**

A **2024 JNCI Cancer Spectrum** meta-analysis (32 studies) reported **~26% lower recurrence** overall, with strongest signals in **post-menopausal** and **ER-positive** survivors; mortality benefits were smaller and clearest around **20–40 mg/day**. Peak recurrence protection appeared around **~60 mg/day** from foods (≈2–3 servings/day)

In Vivo. 2022 Mar 3;36(2):556–562.
Am J Clin Nutr. 2012 Jul;96(1):123-32.
JNCI Cancer Spectr. 2024 Jan 4;8(1):pkad104.

Genistein/Soy Isoflavones

ER-β–selective SERM-like action, modulation of EGFR/HER2 signaling providing estrogenic related relief: bone density, hot flashes, brain fog, joint and muscle pain

Additional Estrogen Modulators

- Iodine
- Flaxseed/Fiber
- Black Cohosh
- Green Tea (EGCG)
- Resveratrol

05

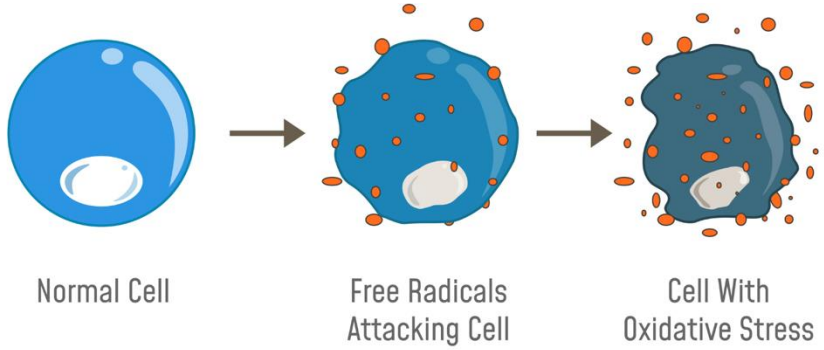
ENZYMES AND PAIN

Immune ←→ Inflammation

White Blood Cells

PRR

MAMP/PAMP, DAMPs



Vasoactive Compounds

- Histamine
- PGE2
- Leukotriene
- Nitric Oxide

Increase Blood Flow
Leukocyte Migration

Activation Leukocytes
Release Cytokines
TNF, IL1, IL6, etc.

Secondary Cellular Signals; i.e. NFkB

Inflammation
Pain

Tissue Destruction

Enzyme Therapy and Immunomodulation

Proteolytic enzymes have a role in immune modulation by modifying surface proteins on T and B cells.

- Trypsin selectively cleaves co-stimulatory molecules — including CD80, CD4, and CD44 — raising the activation threshold required for T-cell signaling.

This rightward shift in activation threshold acts as a biological "reset," dampening hyperactive immune responses and interrupting the inflammatory amplification cascade at the cellular level.

Lehmann PV, Forsthuber T, Miller A, Sercarz EE. Spreading of T cell autoimmunity to cryptic determinants of an autoantigen. Nature 1992; 358: 155-157
Lehmann PV, Sercarz EE, Forsthuber T, Dayan CM, Gammon GG. Determinant spreading and the dynamics of the autoimmune Tcell repertoire. Immunol Today 1993; 14: 203-208
Weiner HL, Friedman A, Miller A et al. Oral tolerance. Ann Rev Immunol 1994; 12: 809-837

Bromelain and Autoimmune Disease

Autoimmune disease fundamentally represents a breakdown in self-tolerance, driven largely by dysregulated CD4+ T cell activity.

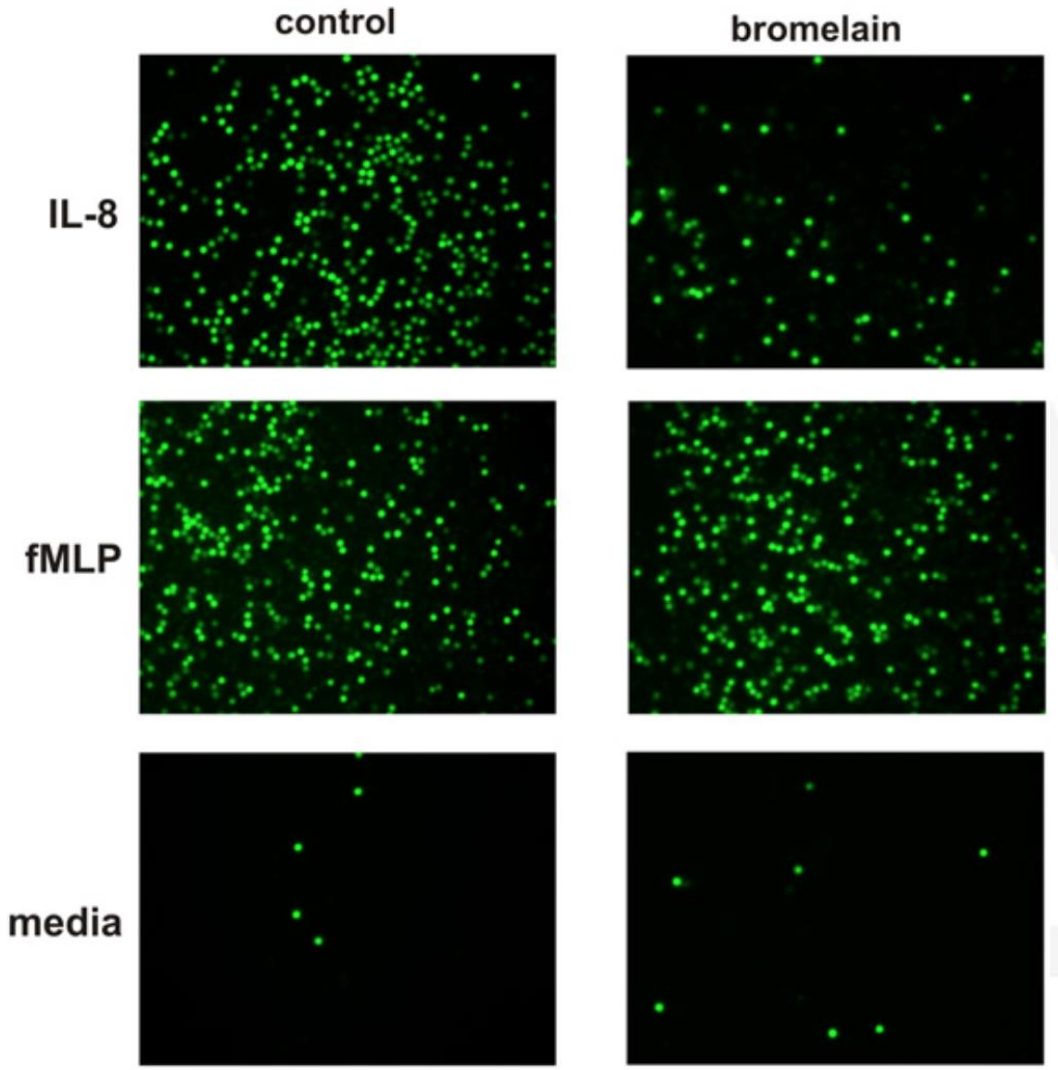
Activated CD4+ T cells → IL-2, triggering a pro-inflammatory cascade that sustains and accelerates autoimmune progression.

- **Bromelain** interrupts this cycle by cleaving CD25, the IL-2 receptor, directly reducing IL-2 signaling and attenuating the downstream inflammatory response at its source.

Bromelain and Inflammation

Bromelain can remove cell surface molecules that may reduce leukocyte trafficking

In vitro studies concluded that there is up to <u>40% reduction</u> in IL-8 signaling of neutrophils when treated with bromelain



Fitzhugh DJ1, Shan S, Dewhirst MW, Hale LP. "Bromelain treatment decreases neutrophil migration to sites of inflammation." *Clin Immunol*. 2008 Jul;128(1):66-74.

Papain and Immunomodulation

JOURNAL OF IMMUNOTOXICOLOGY, 2016
VOL. 13, NO. 4, 590–602
http://dx.doi.org/10.3109/1547691X.2016.1149528

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Anti-inflammatory and immunomodulatory properties of *Carica papaya*

Saurabh Pandey, Peter J. Cabot, P. Nicholas Shaw and Amitha K. Hewavitharana

School of Pharmacy, The University of Queensland, Brisbane, Australia

ABSTRACT
Chronic inflammation is linked with the generation and progression of various diseases such as cancer, diabetes and atherosclerosis, and anti-inflammatory drugs therefore have the potential to assist in the treatment of these conditions. *Carica papaya* is a tropical plant that is traditionally used in the trea
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inflammato
mediators.
papaya are
papaya-ass
clinical stud

ARTICLE HISTORY
Received 14 December 2015
Revised 27 January 2016
Accepted 29 January 2016

Inhibit the release of pro-inflammatory:

- TNFa – 10.8%
- IL-1a, IL-1b – 12.5% and 27.4%
- IL-6 – 42.9%
- IL-8 – 8.4%

Inhibit pro-inflammatory NO induced by IFNy or LPS stimulated macrophages

Enzymes vs. Ibuprofen (NSAIDs)

Treatment of Collagen Induced Arthritis by Proteolytic Enzymes: Immunomodulatory and Disease Modifying Effects

SUBBA R. CHINTALACHARUVU, NANCY URANKAR-NAGY, CHERYL A. PETERSILGE, FADI W. ABDUL-KARIM, and STEVEN N. EMANCIPATOR

ABSTRACT. ***Objective.*** To investigate the efficacy of a novel therapy (proteases) in an animal model of rheumatoid arthritis, and to investigate the mechanisms of arthritogenesis.

Methods. We induced progressive arthritis in male DBA/1 mice by immunization and boosting with Type II collagen; groups of mice were treated orally twice daily with either ibuprofen or proteases, or were left untreated. After 2 weeks, joints were scored for clinical, radiographic, and histologic changes. In addition, we measured serum levels of IgG anti-collagen II, the glycosylation of circu-

Why That Matters

Ibuprofen mainly reduces inflammation symptoms.

Proteases may:

Modulate immune dysfunction

Improve antibody behavior

Slow joint destruction

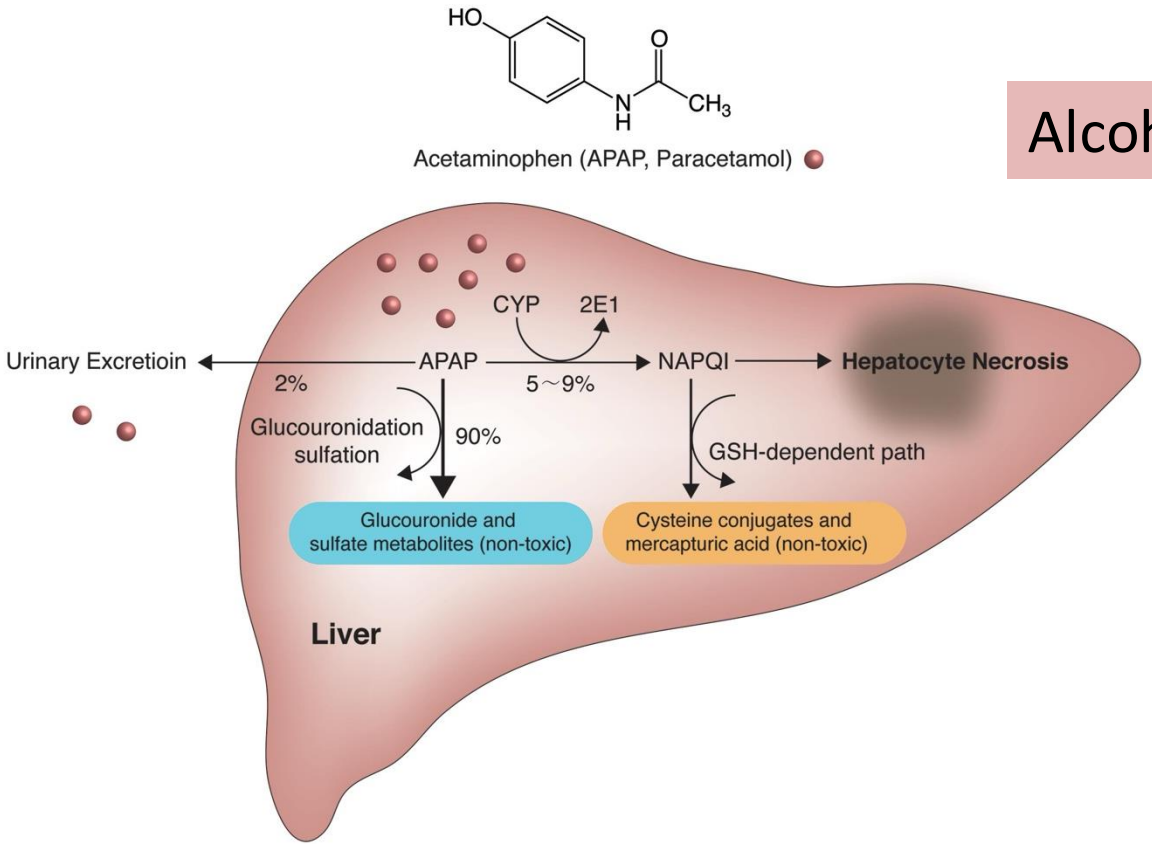
Potentially delay progression to erosive arthritis

Amelioration of joint inflammation, and accentuation of a prototypical Th2 cytokine (interleukin 5) were similar in the ibuprofen and protease treatment groups. However, **protease treatment protects and preserves articular cartilage**, normalizes the sialylation of IgG and anti-collagen antibody, and fully restores Th1 (interferon-gamma) synthesis, distinct from ibuprofen.

Protease therapy has anti-inflammatory efficacy in the early (inflammatory) phase of collagen induced arthritis, similar to ibuprofen. The immunomodulatory effects of proteases, not seen with ibuprofen, may underlie a correction of aberrant IgG glycosylation and/or contribute to the increased capacity of protease to delay or forestall erosive and destructive arthritis or ankylosis. Similar effects may apply to spontaneous RA in humans.

Reactive Intermediate: “Tylenol”

Roughly **50,000–60,000 acetaminophen-related ER visits** occur annually in the U.S., with approximately **half being intentional overdoses**



Alcohol induces 2E1

NAPQI — N-acetyl-p-benzoquinone imine. It's the highly reactive, hepatotoxic metabolite produced when acetaminophen is processed through the **CYP2E1 (and CYP3A4) pathway** in the liver, rather than the safer glucuronidation or sulfation routes.

Side Note: Delivery Method of Enzymes

Controversy surrounds the effectiveness of oral enzymes and their absorptive capacity:

- Oral enzymes have been scrutinized for their vulnerability to digestive acids. Animal based pancreatic enzymes are acid stable and enter the blood stream through intestinal re-absorption (“enterohepatic recycling”)

Bromelain and papain also survive strong acid environments

- Enteric coating and higher dosage enhances survivability

Moskvichyov BV, Komarov EV, Ivanova GP. Study of trypsin thermodenaturation process. Enzyme Microb Tech 8, 498-502, 1986.
Gotze H, Rothman SS. Enteropancreatic circulation of digestive enzymes as a conservative mechanism. Nature 257(5527), 607-609, 1975.
Liebow C, Rothman SS. Enteropancreatic circulation of digestive enzymes. Science 189(4201), 472-474, 1975.

Side Note: Enzymes as a Complimentary Therapy

Proteolytic enzymes may serve as a synergist to traditional cytotoxic agents; either lessening negative effects on the patient or improving effectiveness

- This is also true for Abx such as Amoxicillin

Note: High dose enzyme therapy may produce a high amount of metabolic waste. Support detox, oxidative load and excretion pathways.

Leipner J, Saller R. Systematic enzyme therapy in oncology: effect and mode of action. Drugs. 2000;59:769-780.

Side Note: Enzyme Therapy and Cancer

The following cancers may respond best to proteolytic enzyme therapy.

Pancreatic Cancer: Dense fibrotic/desmoplastic stroma makes drug delivery notoriously poor.

- Enzymes (trypsin, chymotrypsin, bromelain) may degrade stromal and fibrin barriers, improving perfusion and immune penetration.

Breast Cancer: Tends to create fibrin-rich peritumoral capsules and metastatic niches.

- Enzymes may reduce metastatic adhesion and support immune surveillance.

Colorectal Cancer: Often progresses with dense stroma and immune evasion through Tregs and cytokines.

- Enzymes may reduce inflammatory cytokines and normalize adhesion molecules.

Metastatic Cancers with High Fibrin/ECM Deposition: Melanoma, ovarian, and lung cancers often form **fibrin-rich matrices** and immune-shielding environments.

- Enzyme therapy may reduce adhesion molecule expression (ICAM-1, VCAM-1, CD44), impeding metastatic implantation.

06

CLINICAL PEARLS: METABOLISM

Cholecystolithiasis: Gallstones

Yo-yo dieting or weight cycling (repeatedly intentionally losing and unintentionally regaining weight) increases the likelihood of cholelithiasis.

- In a 1999 prospective cohort study of 47,153 women in 11 US states, the risk for cholecystectomy:
  - Increased 20% in “light” cyclers (those who lost and regained 5 to 9 pounds)
  - Increased 70% in “severe” cyclers (those who lost and regained ≥ 20 pounds)
- A 2006 study of US men shows a similar pattern

Syngal S, Coakley EH, Willett WC, et al. Long-term weight patterns and risk for cholecystectomy in women. *Ann Intern Med*. 1999;130(6):471-7.
Tsai CJ, Leitzmann MF, Willett WC, et al. Weight cycling and risk of gallstone disease in men. *Arch Intern Med*. 2006;166(21):2369-74

Walking- Outsized Metabolic Impact

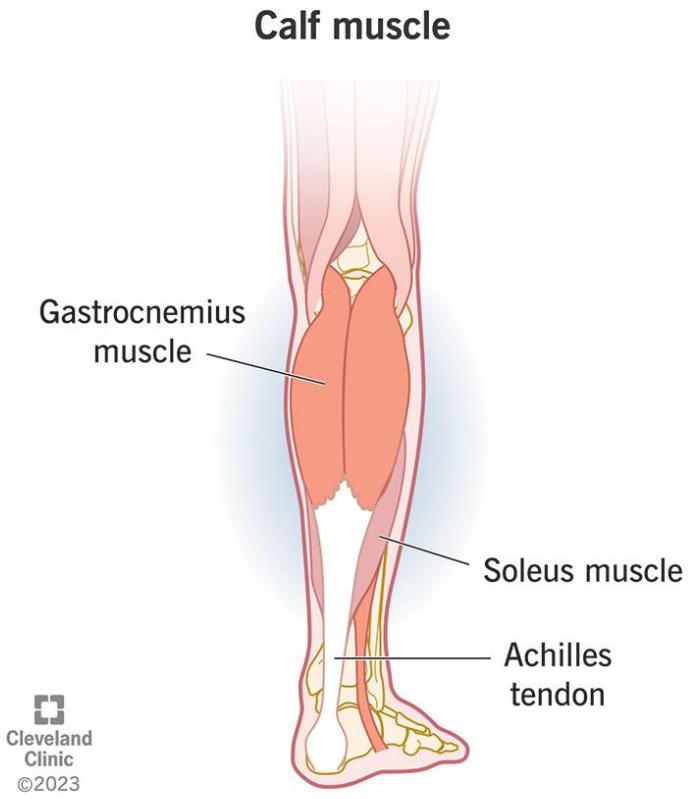
Post-prandial glucose spikes drive insulin resistance and inflammation

- Most adults are sedentary for 8–12 hours/day-
- Average American watches TV/on phone for 6hrs per day

Activity	Rough Average (U.S. adults)
Phone use	~4.5–5.2 hrs/day
Television viewing	~3.7 hrs/day
Total screen time (incl. TV/phones/computers)	~6.5–7+ hrs/day

ConsumerAffairs. “Cell Phone Statistics 2026 [2026]” ConsumerAffairs.com. Jan. 22, 2026, https://www.consumeraffairs.com/cell_phones/cell-phone-statistics.html

Unique Physiology of the Calves



Soleus muscle = 70–90% slow-twitch (Type I) fibers

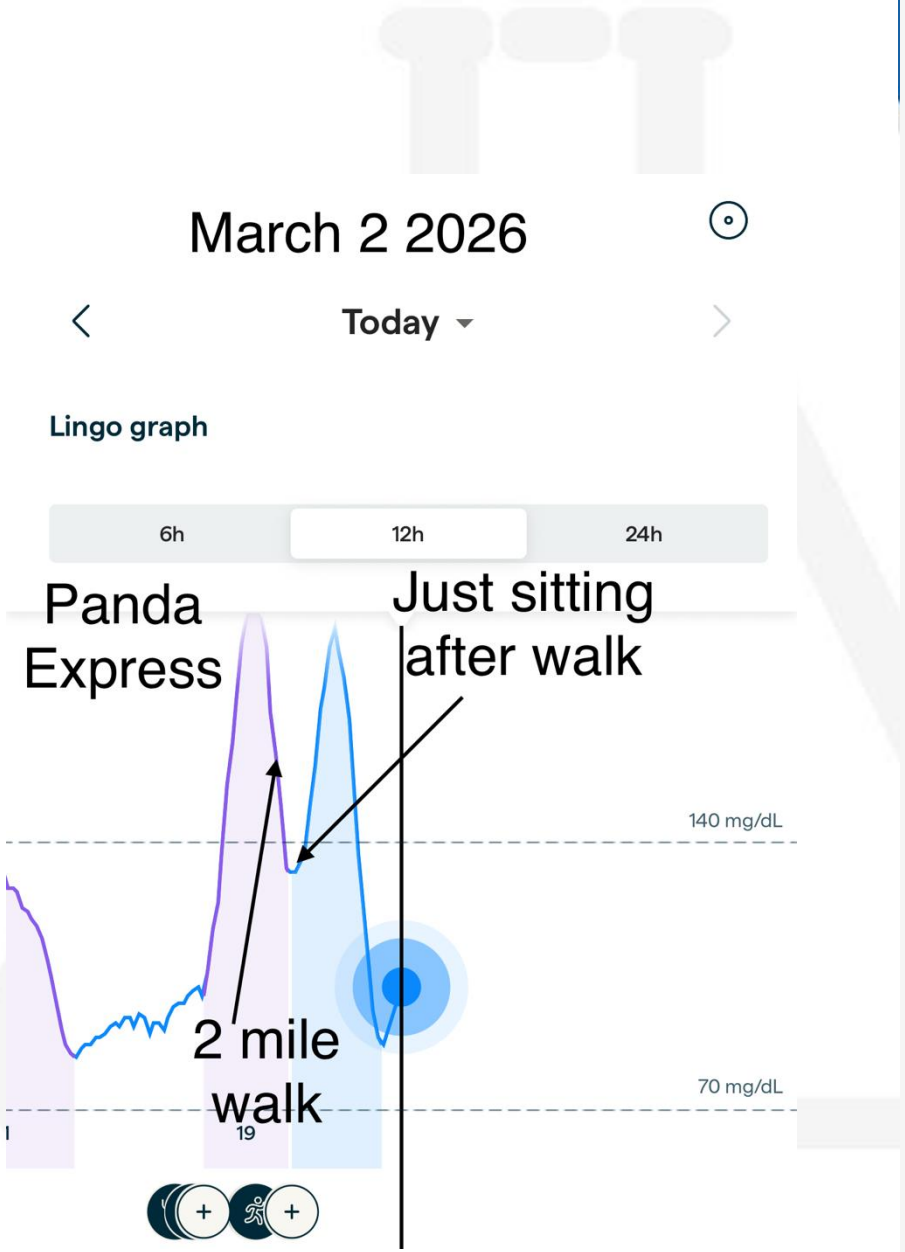
- Type I fibers have **more GLUT4** transporters
- They rely heavily on oxidative glucose metabolism
- **They take up glucose even with very low insulin levels**

- Designed for endurance, posture, and continuous activity
- Preferentially recruited during low-intensity movement

Even light calf activation triggers AMPK signaling, moving GLUT4 transporters to the cell surface, **allowing glucose entry without insulin.**

Clinical Applications

- Post-meal walking (5–15 minutes)
- Desk-based calf raises every 30–60 minutes “calf push-ups”
  - 1–2 minutes of calf raises can measurably lower glucose
- Standing desks or vibration platforms



06

CLINICAL PEARLS: METABOLISM

Fasting and Fasting Mimic Diets

Possible Positive Mechanisms of Fasting

IF produces several characteristic adaptations including **lower blood glucose** and **insulin levels**, **improved insulin sensitivity, increased fatty acid mobilization and ketone body production**, **decreased markers of oxidative stress** and inflammation, enhanced neuroplasticity and neurogenesis, stimulation of autophagy, and increased parasympathetic tone. *Nutrients. 2022 Jun; 14(12): 2536.*

- Alterations in the microbiota
- Eliminating negative interactions with food
- Induction of antioxidant enzymes
- Autophagy/Mitophagy

Free Radic. Biol. Med. 2007;42:665–674.
Int. J. Obes. 2011;35:714–727.
Br. J. Nutr. 2013;110:1534–1547.
Ann. Neurol. 2010;67:41–52.
Free Radic. Biol. Med. 2017;102:203–216.
FASEB J. 2006;20:631–637.
Ageing Res. Rev. 2018;47:183–197.
Brain Behav. 2020;10:e01444.

Fasting Benefits

- Lowers inflammation, including CRP levels
  - Healthy individuals undergoing religious fasting also show reduced levels of pro-inflammatory cytokines including C-reactive protein, tumor necrosis factor -α (TNF-α), interleukin-6 (IL-6), and IL-1β
- Stimulates autophagy, which regulates inflammation, suppresses pro-inflammatory cytokine secretion, and has been implicated in the treatment of inflammatory bowel disease.
- Reduced adipose tissue
- Enhanced synaptic plasticity via increased BDNF
- Increased myelin protein expression resulting in thicker myelin sheath and decreased aberrant Schwann cell proliferation, thus improving peripheral nerve function

Ann. Nutr. Metab. 2007;51:88–95
Nutr. Res. 2012;32:947–955
Nutrition. 2020;79–80:110974.
Autophagy. 2010;6:702–710.
Immunol. Cell Biol. 2013;91:250–258.
Curr. Pain Headache Rep. 2010;14:80–87.
Nutr. Neurosci. 2003;6:11–18.
Brain Res. Dev. Brain Res. 1997;104:131–136.
Best Pr. Res Clin. Rheumatol. 2011;25:141–154.
Ann. Nutr. Metab. 2003;47:194–200.

Fasting Benefits

- Mood enhancement—specifically, increased feelings of well-being, focus, and euphoria
- Release of **norepinephrine**, **epinephrine**, **dopamine**, and **cortisol** in the early phase of fasting with corresponding activation of stress resistance mechanisms → energy and alert
- Increased availability of tryptophan and serotonin in the CNS
- Ketosis-induced neurogenesis, neurotrophic factor synthesis, and expression of neurotransmitter receptors
- **Improved sleep quality**

Ann. Nutr. Metab. 2007;51:88–95
Nutr. Res. 2012;32:947–955
Nutrition. 2020;79–80:110974.
Autophagy. 2010;6:702–710.
Immunol. Cell Biol. 2013;91:250–258.
Curr. Pain Headache Rep. 2010;14:80–87.
Nutr. Neurosci. 2003;6:11–18.
Brain Res. Dev. Brain Res. 1997;104:131–136.
Best Pr. Res Clin. Rheumatol. 2011;25:141–154.
Ann. Nutr. Metab. 2003;47:194–200.

Fasting and Antioxidant Activity

- Reduction in **malondialdehyde**, a well-known by-product of lipid peroxidation
- Fasting increases the activity of key antioxidant enzymes such as **superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), Nrf-2**
- Fasting can decrease the activity of **NADPH oxidase**, an enzyme complex that produces reactive oxygen species (ROS).
- Fasting enhances mitochondrial biogenesis and efficiency.
  - Reduces mitochondrial ROS production, protecting cells from **oxidative damage.**

FASTING Effect on Immunosenescence

(Intermittent, FMD, 24-96hr Fast)

Metabolic Reprogramming- Reduction in Resources/Nutrients

Reduces circulating **senescence-associated secretory phenotype (SASP) factors**

Lowering nutrient and growth signals (glucose, insulin, mTOR), fasting attenuates the accumulation of dysfunctional senescent T-cells and myeloid cells.

Enhanced autophagy helps clear damaged mitochondria and proteins in lymphocytes and antigen-presenting cells. This improves T-cell metabolic fitness and reduces clonal exhaustion.

Cell Metab. 2014;19(2):181-192 doi:10.1016/j.cmet.2013.12.008
Cell Stem Cell. 2014;14(6):810-823. doi:10.1016/j.stem.2014.04.014
N Engl J Med. 2019;381(26):2541-2551. doi:10.1056/NEJMra1905136
Cell Metab. 2015;22(1):86-99. doi:10.1016/j.cmet.2015.05.012
Cancer Cell. 2016;30(1):136-146. doi:10.1016/j.ccell.2016.06.005
Cell. 2019;178(5):1088-1101.e15. doi:10.1016/j.cell.2019.07.049
AMA Intern Med. 2017;177(7):930-938. doi:10.1001/jamainternmed.2017.0936
Proc Nutr Soc. 2017;76(3):361-368. doi:10.1017/S0029665116002986
PLoS One. 2019;14(1):e0209353. doi:10.1371/journal.pone.0209353
Nat Rev Cancer. 2022;22(3):167-185. doi:10.1038/s41568-021-00420-8

06

CLINICAL PEARLS: METABOLISM

GLP Medications

Coming Off GLP-1

Medscape Medical News. Weight regain after stopping GLP-1 receptor agonists may plateau below baseline. Published 2025

48 studies (36 RCTs, 12 observational)

- Up to **3,236 patients modeled**
- Follow-up up to **1-year post-cessation**
- Findings: **Consistent rebound across studies**

Long-term plateau ≈ **75% regain → 25% net loss retained**

Concern: **Disproportionate fat regain**

- → Worse **fat-to-lean ratio** than baseline

Rebound trends suggest:
↑ Blood pressure
↑ Lipids
↑ Inflammatory markers
Worsening glycemic control (if diabetic)

Budini B, Luo S. Weight regain after cessation of glucagon-like peptide-1 receptor agonists: a systematic review and meta-regression analysis. *eClinicalMedicine*.
Rubino DM, Greenway FL, Khalid U, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight maintenance in adults with overweight or obesity (STEP 4). *JAMA*. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224
Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med*. 2021;384(11):989-1002. doi:10.1056/NEJMoa2032183
Liu A, et al. Weight regain and cardiometabolic effects after discontinuation of weight management interventions: a systematic review and meta-analysis. *BMJ*. 2025
Davies MJ, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827

GLP and Body Mass

Lean mass loss on GLP meds: commonly **~25–35% of total weight loss**, sometimes **up to ~40%** without resistance training / adequate protein, and in older/sarcopenic patients.

Bone density: can show **measurable hip/spine BMD decline over ~1 year** in at-risk populations; fracture signal appears in certain subgroups → older females

BMJ Nutr Prev. 2025 Mar 3;8(1):e001206.
Diabetes Obes Metab. 2024;26

Lean Mass Preservation: Creatine

Dosage: 5-20gr per day

- Increases phosphocreatine stores
- Enhances rapid ATP regeneration
- Improves force output during resistance training
- Activates mTOR signaling
- Increased GLUT4 expression
- Neuroprotective

Medical Myths of Creatine

- Hair loss
- Kidney damage
- Fat gain (slight weight gain is common due to intramuscular water retention)
- Causes cramping
- You have to load creatine
- Women shouldn't take creatine

Caloric restriction → lower energy availability

Lower energy → reduced training intensity → muscle loss

Creatine and Cognitive Function

2024

Single dose creatine improves cognitive performance and induces changes in cerebral high energy phosphates during sleep deprivation

Ali Gordji-Nejad[1]✉, Andreas Matusch[1], Sophie Kleedörfer[2], Harshal Jayeshkumar Patel[2], Alexander Drzezga[1,3,4], David Elmenhorst[1,3], Ferdinand Binkofski[2,5,6] & Andreas Bauer[1,6]

The inverse effects of creatine supplementation and sleep deprivation on high energy phosphates, neural creatine, and cognitive performances suggest that creatine is a suitable candidate for reducing the negative effects of sleep deprivation. With this, the main obstacle is the limited exogenous uptake by the central nervous system (CNS), making creatine only effective over a long-term diet of weeks. Thus far, only repeated dosing of creatine over weeks has been studied, yielding detectable changes in CNS levels. Based on the hypothesis that a high extracellular creatine availability and increased intracellular energy consumption will temporarily increase the central creatine uptake, subjects were orally administered a high single dose of creatinemonohydrate (0.35 g/kg) while performing cognitive tests during sleep deprivation. Two consecutive ^{31}P-MRS scans, ^{1}H-MRS, and cognitive tests were performed each at evening baseline, 3, 5.5, and 7.5 h after single dose creatine (0.35 g/kg) or placebo during sub-total 21 h sleep deprivation (SD). Our results show that creatine induces changes in PCr/Pi, ATP, tCr/tNAA, prevents a drop in pH level, and improves cognitive performance and processing speed. These outcomes suggest that a high single dose of creatine can partially reverse metabolic alterations and fatigue-related cognitive deterioration.

Study Design

- A double-blind, randomized crossover trial in 15 healthy adults.
- Participants stayed awake for ~21 hours (sleep deprivation) and received **either a single high oral dose of creatine monohydrate (0.35 g/kg body weight)** or placebo on separate nights.

Interpretation

A **single, large dose of creatine** can acutely alter brain high-energy phosphate metabolism during extended wakefulness, helping **maintain cognitive performance and partially counteract fatigue-related declines**.

This suggests creatine uptake into the central nervous system can occur rapidly when the brain's energy demand and extracellular availability are high.

Gordji-Nejad, A., Matusch, A., Kleedörfer, S. *et al.* Single dose creatine improves cognitive performance and induces changes in cerebral high energy phosphates during sleep deprivation. *Sci Rep* 14, 4937 (2024)

Metrics to Monitor on GLP Medications

Body Composition

- DXA Body Comp
- Biometric scale
- Measurements

Heart Rate Variability (HRV)

- Some will “adapt”
- Usually, worse immediately following injection

33 Markers to Monitor GLP-1 Medication

This is a FASTING Blood Panel

Liver/Kidneys: ALT, AST, Protein, Albumin, Globulin, Alkaline Phosphatase, Bilirubin, GGT, Carbon Dioxide, BUN, Creatine, GFR

Electrolytes: Potassium, Calcium, Sodium, Chloride, Magnesium (RBC)

Nutrients: Iron Panel, Ferritin, Homocysteine, Vitamin D

Pancreas: Lipase

Mini Thyroid: TSH, Free T4, Free T3

Metabolic/Sugar: Glucose, HbA1c, Insulin

GLP and Motility

Early treatment:

- Significant delay in gastric emptying

Chronic use:

- Effect attenuates
- Central appetite suppression becomes dominant

Soluble Fiber

- Synergistic combo with GLP-1 to improve satiety
- Reduces nausea by improving glycemic stability
- Enhances endogenous GLP-1 → can use lower dosages

Insoluble Fiber

- Bulks stool to promote peristalsis

Must start slow- 5g per day to assess tolerance on GLP-1
Fiber can significantly slow motility in some patient; not a favorable addition to GLP
Patient must drink enough water or they WILL become constipated

GLP and Electrolyte Maintenance

Mechanisms

- Reduced electrolyte intake
- GLP receptors present in kidneys
  - ↑ Renal sodium excretion
  - ↑ Mild diuresis
  - ↓ Intravascular volume (early phase)
- May lower magnesium status

07

FATIGUE: BOREDOM (MENTAL AROUSAL) V. FATIGUE

~~“I’m Bored”~~ --> “I’m tired all the time”

I feel good at work, but as soon as I get home, I crash on the couch

I have plenty of energy at the gym but can fall asleep any other time of the day

Walking throughout the day helps my energy

Mechanistic Drivers

- Low novelty
- Low dopamine tone
- Excess screen stimulation blunting reward circuits
- Overexposure to fast reward cycles
- Psychological disengagement
- Under-challenged cognition

Fatigue vs. Boredom vs. Depression

Feature	Fatigue	Boredom	Depression
Energy improves with excitement?	❌	✅	Often
Post-exertional crash?	✅	❌	Rare
Heavy limbs feeling?	Common	Rare	Sometimes
Anhedonia?	No	No	Yes
Hopeless thoughts?	No	No	Yes
Lab abnormalities?	Often	Rare	Sometimes inflammatory markers
Wants to do things?	Yes	Yes	Often no

Dopamine

Dopamine Powder: 1tsp 2x per day

EGCG: 1 with ea. Dose of **Dopamine Powder**

May help to balance oxidative stress in the brain, preserves dopamine and metabolites through various mechanisms

Pyridoxial-5-Phosphate (P-5-P): 20-60mg per day; Cofactor in dopamine synthesis

L-Tyrosine: precursor to dopamine

Curcumin: reduction in neuro-inflammation and inhibits MAO

- Effort willingness
- Anticipation
- Drive
- Engagement
- Movement initiation

Journal of Movement Disorders 2024;17(3):357-359.
Image: *Translational Psychiatry* volume 12, Article number: 464 (2022)
Indian J Pharm Sci. 2010 Mar-Apr;72(2):149–154.

Prolactin and Dopamine

Prolactin is an indirect dopamine marker

Prolactin is produced by **lactotroph cells** in the anterior pituitary.

Unlike most pituitary hormones (which are stimulated by the hypothalamus), prolactin is **tonically inhibited by dopamine**.

High prolactin → low dopamine tone

Low prolactin → high dopamine tone

Histamine and Dopamine

Histamine regulates dopamine release through the **H3 receptor** → presynaptic inhibitory receptor on dopaminergic neurons.

When histamine activates H3 receptors, it **suppresses dopamine release and signaling**, particularly in the **basal ganglia and cortex**, which can affect motor control, arousal, and attention.

*"Benadryl (*diphenhydramine*) my symptoms worse"*
Blocking H1 shifts signaling toward H3-mediated dopamine suppression in the basal ganglia

This is why elevated histamine has been linked with:

- **Dystonia**
- **Tourette's**
- **Restless leg syndrome**
- **Tics**
- **Parkinsonian symptoms**

Date Collected: **02/05/2026**

GGT

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
GGT [02]	25		IU/L	0-65

Histamine Determination, Blood

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
▲ **Histamine Determination, Blood** [B, 01]	**228** **High**		ng/mL	12-127

Thyroglobulin Antibody

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Thyroglobulin Antibody [04]	<1.0		IU/mL	0.0-0.9

Thyroglobulin Antibody measured by Beckman Coulter Methodology

Histamine Testing

Whole blood histamine- reflects **histamine stored in basophils over time**, making it more useful for assessing **chronic histamine burden or histamine intolerance patterns**.

Clinical Pearl: less impacted by anti-histamines

Plasma histamine- **Plasma histamine** reflects **recent or acute histamine release** (minutes to hours) and is typically ordered when evaluating **mast cell activation or allergic reactions**.

Histamine Testing

Tryptase- A proteolytic enzyme stored almost exclusively in mast cell granules. Elevated serum tryptase — particularly when drawn within 1–2 hours of a reaction is a strong indicator of mast cell degranulation. Persistently elevated baseline tryptase may suggest systemic mastocytosis or hereditary alpha-tryptasemia.

Clinical Pearl: The gold standard marker for confirming anaphylaxis and mast cell activation

Urinary N-Methylhistamine- The primary urinary metabolite of histamine. Because it is collected over 24 hours, it reflects total histamine turnover and mast cell activity over time — less susceptible to acute fluctuations than plasma histamine.

Clinical Pearl: Preferred for evaluating chronic mast cell activation syndrome (MCAS)

Urinary Prostaglandin D2 (PGD2) / Prostaglandin E2 (PGE2)- Prostaglandin D2 is the dominant prostaglandin released by mast cells during degranulation. Its urinary metabolite (11β-PGF2α) serves as a stable marker of mast cell activity. PGE2 elevation reflects broader inflammatory and mast cell-driven eicosanoid production.

Clinical Pearl: Useful when tryptase is normal but MCAS is still clinically suspected

Histamine Testing

Diamine Oxidase (DAO)- The primary enzyme responsible for breaking down ingested histamine in the gut. Low DAO activity indicates impaired histamine degradation — a key mechanism in histamine intolerance. Useful when symptoms are diet-triggered rather than mast cell-driven.

Clinical Pearl: Distinguishes histamine intolerance from true mast cell activation

Serum IgE (Total and Specific)- Reflects allergic sensitization. Elevated total IgE suggests atopic background; specific IgE identifies individual triggers. Mast cells are IgE-coated, repeated antigen exposure drives degranulation.

Clinical Pearl: Normal IgE does not rule out MCAS, non-IgE mast cell activation is common

Chromogranin A (CgA) A neuroendocrine and mast cell co-secretory marker. Elevated in systemic mastocytosis and neuroendocrine tumors. Useful when the clinical picture is unclear. Clinical Pearl: Must account for PPI usem PPIs falsely elevate CgA

Histamine Testing

Heparin (Plasma)- Mast cell granules co-release heparin with histamine and tryptase. Elevated plasma heparin can support mast cell degranulation, particularly in systemic or aggressive mastocytosis.

Urinary Leukotriene E4 (LTE4)- Another mast cell-derived eicosanoid. Complements PGD2 when building a comprehensive MCAS biomarker panel.

Clinical Pearl: Particularly relevant in aspirin-exacerbated respiratory disease and MCAS overlap

Mental Arousal

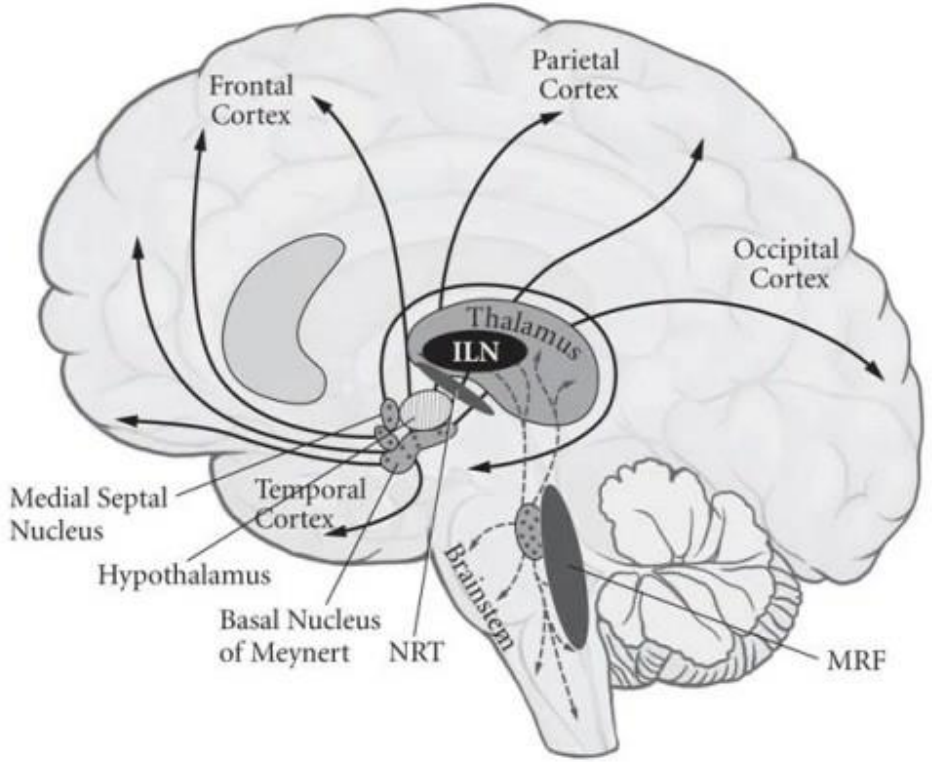
Mental arousal is the brain's **state of alert readiness,** the degree to which the nervous system is activated and prepared to process information, respond, and act.

It exists on a spectrum:

- Low arousal → sleepiness / disengagement
- Optimal arousal → focus / clarity
- High arousal → anxiety / hypervigilance

It is regulated primarily by:

- Dopamine
- Norepinephrine
- Acetylcholine
- Orexin (hypocretin)
- Reticular activating system (RAS)



Acetylcholine

Cholinergic neuromodulation is pivotal for arousal, attention, and cognitive processes → **post ganglion neurons**. Negative experiences have a more visceral memory pattern vs. positive.

Acetylcholine also drives the release of of dopamine and norepinephrine

Phosphatidylcholine: 2-6 (1,000-2,000mg per day)

Acetyl L Carnitine: 2 b.i.d. (1,000, 2,000mg per day)

NAC: 1-4 (500-4,000mg per day)

Gingko Biloba: 3 per day (120mg per day)

Myo + D Chiro Inositol: 1 heaping tsp. b.i.d; helps choline availability

Nicotine Tob Res. 2019 Jan 25;22(2):152–163.
Nature **volume 621**, pages577–585 (2023)

Sleep and Neuroplasticity

Sleep is when the brain undergoes most of its neuroplastic changes, and this process is tightly coupled to memory consolidation, emotional regulation, synaptic remodeling, and metabolic restoration.

When to Dose Products for Neuroplasticity

Most products should be dosed in a “plasticity window”; Dosed prior, duration and for a short duration afterwards

- Phase 1: Products that create alertness → Caffeine, ginseng, etc.
- Phase 2: Increase Ach, Dopamine

The essence of plasticity is to create a window of attention and focus that's distinct from the rest of the patient’s day

Basic Neurology Support

Omega 3 and Pro Resolvins

N-Acetyl Cysteine

SAMe

Medium Chain Triglycerides

Magnesium

DHEA

Pregnenolone

Stress vs. Anxiety

Stress *(Autonomic Arousal)* 😃

- Increased alertness (arousal)
- Increase cognition and focused attention
- Suppression of appetite
- Increased respiratory rate
- Increase pulse and BP
- Increased gluconeogenesis and lipolysis
- Increased pain threshold
- Decreased gastric motility

Outcomes: Higher level problem solving and sense of accomplishment and reward, positive neuroplastic changes

Anxiety *(dysfunctional/dysregulated)* 😟

- Rapid respiration
- Elevated heart rate not justified by magnitude of stimulus
- Muscle tension
- Disorganized firing patterns → dizzy, foggy, lightheaded
- Worry, dread
- Reclusive
- Increased gastric motility

Outcomes: Fear of reoccurring stimulus, rumination, reinforcement of negative emotions

08

RE-VISTING MELATONIN

High Dose Melatonin and Pineal Gland Suppression?

Long-term use (months to years): Most human and animal studies suggest **no permanent suppression** of pineal function, but a short period of “downregulation” in secretion amplitude can occur, typically normalizing within **a few days to 2 weeks** after cessation.

Very high doses (>10 mg nightly) have not been linked to lasting suppression but may cause more transient disruption in timing (phase shift) rather than total output.

Matsumoto M, Sack RL, Blood ML, Lewy AJ. The amplitude of endogenous melatonin production is not affected by melatonin treatment in humans. *J Pineal Res.* 1997;22(1):42-44.

Givler D. Chronic administration of melatonin: Physiological and … *PMCID*. 2023. **(Narrative review summarizing safety and lack of long-term suppression with low-to-moderate doses.)**

InpharmD Researcher. Does supplemental melatonin suppress endogenous melatonin production? *InpharmD.com*. **(Majority of studies suggest long-term use does not suppress endogenous production.)**

Moon E, et al. Safety issues regarding melatonin use in child and … *Kosin Med J.* 2022; **(Long-term studies in children/adolescents show no evidence of inhibited natural secretion.)**

Hardeland R. Divergent importance of chronobiological considerations … *Int J Mol Sci.* 2021;9(1):18. **(Very high doses used for antioxidative/anti-inflammatory purposes; no evidence of severe circadian clock disturbance.)**

Arendt J. Melatonin: Countering chaotic time cues. *Front Endocrinol (Lausanne).* 2019; **(High pharmacological doses unlikely to cause desensitization or lasting circadian disruption.)**

Melatonin and Breast cancer

- A potent antioxidant that scavenges free radicals and enhances the activity of other antioxidant enzymes.
- Can downregulate the expression of estrogen receptors and inhibit the enzyme aromatase, which converts androgens to estrogens.
- Influences cell cycle regulation and promotes apoptosis (programmed cell death) in cancer cells.
- Can modulate immune responses by enhancing the activity of natural killer (NK) cells and cytotoxic T lymphocytes.
- Inhibits angiogenesis (formation of new blood vessels) and the expression of metastasis-related genes.
- Enhance the efficacy of chemotherapy and radiation therapy while reducing their side effects.

Neuroendocrinology Letters, 23(Suppl 1), 30-38.
Advances in Experimental Medicine and Biology, 429, 593-604.
British Journal of Cancer, 71(4), 854-856.
Trends in Endocrinology and Metabolism, 20(5), 225-233
Neuroimmunomodulation, 15(3), 190-196.
Integrative Cancer Therapies, 11(4), 293-303.

Melatonin and Mitochondria

Melatonin and the Optics of the Human Body

Scott Zimmerman*[1] and Russel J. Reiter[2]

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[2]Department of Cell Systems and Anatomy UT Health Science Center San Antonio, Texas, 78229 USA

2019

"It has now been shown that the mitochondria produce melatonin in many cells in quantities which are **orders of magnitude higher than that produced in the pineal gland** . This subcellular melatonin does not necessarily fluctuate with our circadian clock or release into the circulation system but instead has been proposed to be consumed locally in response to the free radical density within each cell, in particular in response to Near Infrared (NIR) exposure. The main point of this review hypothesizes that the subcellular melatonin is being produced in response to the NIR photons which make up the majority of natural sunlight.

Given the number of cells and quantity of subcellular melatonin identified to date, it is reasonable to propose that the body produces and maintains a melatonin reservoir that is separate and apart from the circulatory melatonin generated by the pineal gland. "

Melatonin “Nighttime Guardian” Against Alzheimer’s Disease

Melatonin: 3-20mg; 60-120min before bed

- Enhances deep sleep → improves amyloid/tau clearance
- Reduces oxidative damage → protects neurons
- Modulates microglia → lowers inflammation
- Stabilizes mitochondria → preserves energy metabolism
- Maintains circadian rhythm → prevents pathology cascade

THANK YOU

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Facebook: FaceBook.com/drugfreedoctor

Gateway Natural Medicine
& Diagnostic Center