

Anti-Aging Medicine & Male and Female Hormones

Michelle Leary-Chang, ND, IFMCP

Disclosures

- Medical Consultant for Metagenics Inc.
- Director of Functional Medicine for Vida Integrated Health
- Certified practitioner through the Institute for Functional Medicine (IFMCP)
- I am <u>very</u> biased that food is medicine...

1

Today's Topics

- 1) Anti-Aging Medicine: Inflam-Aging, Mitochondria, Laboratory Diagnostics and Interventions to Consider
- 2) Women's Hormones: Menopause and beyond
- 3) Men's Hormones: Approach to optimization of testosterone and the aging male

What is Anti-Aging Medicine?

"Anti-aging medicine is an evolving branch of medical science and applied medicine. It treats the <u>underlying</u> <u>causes of aging</u> and aims at alleviating any age related ailment"

Indian J Plast Surg. 2008 Oct; 41(Suppl): S130-S133.

3

Anti-Aging Medicine is more than...

- Aesthetic treatments
- Reconstructive surgery
- Botox and Filler
- Peptide therapies

But if that's what you choose to do... No judgement here.

These therapies work BETTER when your cells are healthy and vibrant.





Don't forget the basics

Sleep

Nutrition

Exercise

Stress Management

Supportive relationships

Healthy Aging = Healthy Gut = Healthy Detox





Mechanisms Behind Aging

- Inflammation: The immune response to stress
- Oxidative Stress: Cellular free radical attack
- **Blood sugar and Insulin Balance:** Why insulin balance is key to managing aging signals
- Hormones: Hypothalamic-Pituitary-Adrenal-Thyroid- Gonadal
- Telomeres and Epigenetics: Our DNA and its role in aging

7

My Top 3 : Anti-Aging Approach

#1 Reduce inflammation and treat insulin resistance

#2 Optimize mitochondrial function, density, and resilience

#3 Get your hormones right... Sex hormones, stress hormones, metabolic hormones... ALL OF THEM!

** GI and Detox system health is essential otherwise you will be chasing 1, 2, and 3!! **



The Immune Response and Inflammation

What IS a Healthy Immune Response ??

Responsive

Detects a threat and recruits innate immune cells through cytokine signaling to the damaged cell or tissue.

Regulated

The response does not exceed the required attention.

Resilient

The immune system repairs and soothes tissue damaged as a result of initial insult

Tolerant

The cells targeted for elimination are not self-tissue and the immune system closely regulates its need for continued response

Current world circumstances makes this very relevant!!

11



Kulkarni OP, Lichtnekert J, Anders H-J, Mulay SR. The Immune System in Tissue Environments Regaining Homeostasis a "Inflammation" Always Inflammation? *Mediators of Inflammation*. 2016;2016:1-9. doi:10.1155/2016/2856213



My Top 3 : Anti-Aging Approach

#1 Reduce inflammation and treat insulin resistance

#2 Optimize mitochondrial function, density, and resilience

#3 Get your hormones right... Sex hormones, stress hormones, metabolic hormones... ALL OF THEM!



Silva FPD, Machado MCC. Septic Shock and the Aging Process: A Molecular Comparison. Frontiers in Immunology. 2017;8. doi:10.3389/fimmu.2017.01389



Barnes PJ, Karin M. Nuclear Factor-KB – A Pivotal Transcription Factor in Chronic Inflammatory Diseases. New England Journal of Medicine. 1997;336(15):1066-1071. doi:10.1056/nejm199704103361506

Macrophage and Neutrophil Recruitment and Activation



Murphy, Kenneth M., Janeway's Immunobiology, 8th Edition (Immunobiology: The Immune System (Janeway)) (p. 3). Taylor and Francis CRC ebook account. Kindle Edition.

NF-kB Activation: Positive Feedback Loop



Barnes PJ, Karin M. Nuclear Factor-κB – A Pivotal Transcription Factor in Chronic Inflammatory Diseases. New England Journal of Medicine. 1997;336(15):1066-1071. doi:10.1056/nejm199704103361506

Take Home Point!

Chronic inflammation is stimulated by dysfunction in the immune response

Too much **R**ESPONSE

Too little **R**EGULATION AND **R**ESILIENCE

19

What does this have to do with AGING??



Insulin Resistance





Insulin Resistance = Inflammation: Two Way Street to Aging

1) Over eating= more fat deposition = obesity

2) Cellular "necrosis" death or cellular zombie state "senescence" leads to inflammation turning ON

3) Insulin Resistance in fat cells and liver cells encourages MORE inflammation (feedback LOOP - Think NF-kB slide!!)

4) Insulin Resistance in muscle tissue leads to reduced sensitivity

23



Metabolic Inflammation

Lima LCF, Braga VDA, Maria Do Socorro De França Silva, et al. Adipokines, diabetes and atherosclerosis: an inflammatory & 2015;6. doi:10.3389/fphys.2015.00304

Take Home Point!

Inflammation drives Insulin Resistance and Insulin Resistance drives Inflammation.

They are CO-ACTIVATORS of each other



Remember...My Top 3: Anti-Aging Approach

#1 Reduce inflammation and treat insulin resistance

#2 Optimize mitochondrial function, density, and resilience

#3 Get your hormones right... Sex hormones, stress hormones, metabolic hormones... ALL OF THEM!

Mitochondria and Healthy Aging



Mitochondria and Healthy Aging



<text>

Palikaras K, Daskalaki I, Markaki M, Tavernarakis N. Mitophagy and age-related pathologies: Development of new therapeutics by targeting mitochondrial turnover. Pharmacology & Therapeutics. 2017;178:157-174. doi:10.1016/j.pharmthera.2017.04.005

Mitochondrial DNA vs Nuclear DNA

Mitochondrial DNA

Maternally inherited

Very susceptible to damage from ROS

Poor damage repair capabilities

Mutation rate is high

Nuclear DNA

Inherited from both parents

Protected from ROS

Ability to repair damaged DNA

Low mutation rate

Byun H-M, Baccarelli AA. Environmental exposure and mitochondrial epigenetics: study design and analytical challenges. *Human Genetics*. 2014;133(3):247-257. doi:10.1007/s00439-013-1417-x

Cell

Mitochondrial DNA

Mitochondria



Take Home Point!

Mitochondria are essential for life, and healthy aging. If they become dysfunctional so does the cell they inhabit.

Increasing Mitohormesis with healthy stressors can enhance protection and repair of the Mitochondria

Before we jump into hormones...



Fancy Terms you NEED to KNOW

Senescence

- mTOR (Mammalian or mechanistic target of rapamycin)
- *Sirtuins
- Autophagy
- AMPK (AMP activated protein kinase)

- ✤ Telomeres
- Oxidative Stress/ ROS



Senescence: AKA Zombie Cells



Senescence is defined as the cell's loss of the ability to divide and induce apoptosis when appropriate.

This leads to increased inflammation, ROS, and prompting neighboring cells to become senescent.

Ogrodnik M, Salmonowicz H, Gladyshev VN. Integrating cellular senescence with the concept of damage accumulation in aging: Relevance for clearance of senescent cells. Aging Cell. 2018;18(1). doi:10.1111/acel.12841

Mechanisms of Cellular Senescence



Hoare M, Das T, Alexander G. Ageing, telomeres, senescence, and liver injury. *Journal of Hepatology*. 2010;53(5):950-961. doi:10.1016/j.jhep.2010.06.009

mTOR (Mammalian Target of Rapamycin)



hyperactivation

Stallone G, Infante B, Prisciandaro C, Grandaliano G. mTOR and Aging: An Old Fashioned Dress. International Journal of Molecular Sciences. 2019;20(11):2774. doi:10.3390/ijms20112774

mTOR (Mammalian Target of Rapamycin)

mTOR activators

Glucose, insulin, and signals for growth and nutrient excess Mitochondrial dysfunction Inflammation Toxic chemicals namely BPA and parabens (directly can activate mTOR)

Over activation of mTOR

Inflammation and autoimmunity if the resistance to death signals is not turned off.

Association with cancer

Adipogenesis and lipogenesis

Bacterial endotoxemia

Reduction of autophagy



Stallone G, Infante B, Prisciandaro C, Grandaliano G. mTOR and Aging: An Old Fashioned Dress. International Journal of Molecular Sciences. 2019;20(11):2774. doi:10.3390/ijms20112774

Sirtuins: A Mitochondria's best friend



"Modulation of sirtuin activity in mammals can regulate many processes such as gene expression, cell metabolism, apoptosis, DNA repair, cell cycle, development, immune response and neuroprotection"

Grabowska et al., 2017

Favero G, Franceschetti L, Rodella LF, Rezzani R. Sirtuins, aging, and cardiovascular risks. *Age*. 2015;37(4). doi:10.1007/s11357-015-9804-y Grabowska W, Sikora E, Bielak-Zmijewska A. Sirtuins, a promising target in slowing down the ageing process. *Biogerontology*. 2017;18(4):447-476.

40



Sirtuins are activated in the presence of molecule NAD+

This molecule is generated in the fasting state or with exogenous NAD administration

Guarente L. The resurgence of NAD+. Science. 2016;352(6292):1396-1397. doi:10.1126/science.aag1718





AMPK and Insulin Resistance



Ruderman NB, Carling D, Prentki M, Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. Journal of Clinical Investigation. 2013;123(7):2764-2772. doi:10.1172/jci67227

Autophagy: The Antidote to Senescence



Stead ER, Castillo-Quan JI, Miguel VEM, et al. Agephagy – Adapting Autophagy for Health During Aging. Frontiers in Cell and Developmental Biology. 2019;7. doi:10.3389/fcell.2019.00308

Autophagy: Mechanisms of Activation

"Of all the nutrientassociated signaling molecules, mammalian target of rapamycin (mTOR) has been shown as one of the key upstream modulators of autophagy signaling"

Chung KW, Chung HY. The Effects of Calorie Restriction on Autophagy: Role on Aging Intervention. Nutrients. 2019;11(12):2923. doi:10.3390/nu11122923

Autophagy elongation

46

Oxidative Stress and ROS and Aging



ROS produced from inflammatory responses, insulin resistance, DNA damage, and drives metabolic dysfunction aggravating further aging processes

Silva FPD, Machado MCC. Septic Shock and the Aging Process: A Molecular Comparison. Frontiers in Immunology. 2017;8. doi:10.3389/fimmu.2017.01389



Telomeres

- Telomeres are cap-like structures on the tips of chromosomes which shorten with age and accelerated cell division.
- Telomeres can be maintained through the enzyme telomerase.
- Anti-aging strategies helps to maintain or slow the degradation of telomere loss

48

Take Home Point!

There is a complex molecular network of signals that affects longevity genes, inflammation processes, and stimulates cellular repair.

Understand these and it will serve you and your patients =)

Lab Testing



Basic Anti-Aging Laboratory Diagnostics

CBC and Chemistries	Lipid Panel
Thyroid Panel	RBC Magnesium
HsCRP	Coenzyme Q10
Fibrinogen	Ferritin & Iron Panel
Insulin Resistance Panel & HbA1c	Homocysteine
Vitamin D	MMA, B12, and Folate
Omega 3 Fatty Acid Profile	Serum Hormones*** (stay tuned)

Advanced Anti-Aging Laboratory Testing

Functional Stool Analysis (when appropriate / possible)

Metabolite and/or Nutrient Profile with Amino Acids, organic acids, and oxidative stress markers

Cortisol Salivary Profile

Sex Hormone Testing (serum or urine)



When to use Functional Stool Analysis

Inflammation starts in the GUT for many

If the gut is dysbiotic, inflamed, overly "permeable", etc... Your antiaging therapies WILL be blunted if you don't address this!!

Patient reports GI complaints: E.g. Gas, bloating, diarrhea, constipation, intolerance to sugar, multiple food sensitivities, etc

Poor detoxification pathways, elevated liver enzymes, etc

58



Advanced Functional Nutrient and Metabolite Analysis



When to use Advanced Metabolite & Nutrient testing

Basic panels came back perfect and you're looking for ways to further optimize

Patient's healthy diet and lifestyle habits are already well established

Patient requests advanced testing and you are comfortable ordering

Examples of Advanced Lab Work-Up

		Detox	cificati	ion Impairment		
Methionine	4	Glycine		Serine		Taurin
Glutamine		Pyroglutamate	1	Sulfate		Benzo
Low Significance						
		Oxidative Str	ess/A	ntioxidant Insufficiend	=y	
Taurine		Selenium		Lead		Mercu
alpha-Tocopherol		gamma-Tocopherol		Vitamin A (Retinol)		β-Cari
Lipid Peroxides		8-OHdG*		p-Hydroxyphenyllactate	1	Sulfat
Low Significance						
Low Significance		Mitochond	rial Fu	unctional Impairment		
Low Significance Magnesium	Ļ	Mitochond Coenzyme Q10	rial Fu	Inctional Impairment Adipate	1	Suber
Low Significance Magnesium Ethylmalonate	↓ †	Mitochond Coenzyme Q10 Pyruvate	rial Fu	unctional Impairment Adipate L-Lactate	† †	Suber a-Hyd

osine, Tryptophan, B6, Antioxidants)		16	3.9
Vanilmandelate	3.8	H I	· · · · •
Homovanillate	4.3	1.9	5.7
5-Hydroxyindoleacetate	6.8	2.1	5.6
Kynurenate	11		1.0
Quinelinate	2.6		4.0
Quincimate	2.0		8.0
Picolinate	5.6		
dative Damage and Antioxidant min C and Other Antioxidants)	Markers		0.29
p-Hydroxyphenyllactate	0.47	++	
8-Hydroxy-2-deoxyguanosine s for 8-hydroxy-2-dexoyguanosine are ng/r	4,9 ng creatinine)	H	5.3
8-Hydroxy-2-deoxyguanosine s for 8-hydroxy-2-dexoyguanosine are right oxification Indicators	4,9 ng creatinine) Tox	icants and Detoxific	sation
8-Hydroxy-2-deoxyguanosine is for 8-hydroxy-2-deoxyguanosine are right oxification Indicators , NAC, Met, Mg, Antioxidants)	4.9 ng creatinine) Tox	icants and Detoxific	5.3 ation
8-Hydroxy-2-deoxyguanosine is for 8-hydroxy-2-deoxyguanosine are right oxification Indicators , NAC, Met, Mg, Antioxidants) 2-Methylhippurate	4.9 ng creatinine) Tox 0.111	icants and Detoxific	53 ation
8-Hydroxy-2-deoxyguanosine s tor 8-hydroxy-2-deoxyguanosine are ngtr oxification Indicators NAC, Mer, Mg, Antioxidants) 2-Methylhippurate Orotate	4.9 ng creatinine) Tox 0.111 0.57	icants and Detoxific	53 ation 0.084 1 1 € 0.09 1 0 000 1 0 000 1
8-Hydroxy-2-deoxyguanosine s tor 8-hydroxy-2-deoxyguanosine are rept oxification Indicators , NAC, Mer, Mg, Antoxismit) 2-Methythippurate Orotate Glucarate	4.9 ng creatinine) 0.111 0.57 9.9	icants and Detoxific	53 53 53 53 53 53 53 53 53 53
8-Hydroxy-2-deoxyguanosine tor 8-hydroxy-2-deoxyguanosine ar ngin oxification Indicators ,NAC, Mc, Mg, Antoxisians) 2-Methythippurate Orotate Glucarate o-Hydroxybutyrate	4.9 ng creatinine) 0.111 0.57 9.9 <dl< td=""><td>icants and Detoxific</td><td>t 53 sation 0066 0066 006</td></dl<>	icants and Detoxific	t 53 sation 0066 0066 006
8-Hydroxy-2-deoxyguanceire ar not siz 8-hydroxy-2-deoxyguanceire ar not costfication Indicators and the state of the state of the cost of the state of the state of the state of the cost of the state of the state of the state of the cost of the state of the state of the state of the cost of the state of the state of the state of the cost of the state of the state of the state of the state of the cost of the state of the state of the state of the state of the cost of the state of the state of the state of the state of the cost of the state of the cost of the state of the cost of the state of th	4.9 ng creatinine) 0.111 0.57 9.9 <dl 67</dl 	icants and Detoxific	sation
8-Hydroxy-2-deoxyguanosine tor 8-hydroxy-2-deoxyguanosine ar nghr oxification Indicators ,A4C, Me, Mg, Antoesdantg) 2-Methylhippurate Orotale Glucarate a-Hydroxybutyrate Pyrroglutamate	4.9 ng creatinine) 0.111 0.57 9.9 <dl 67</dl 	icants and Detoxific	0.094 0.094 0.09 0.00

Cortisol and Adrenal Testing



Salivary Cortisol Testing and Adrenal Markers



Useful but not necessary all the time

Sleep dysregulation, anxiety, and fatigue are the biggest reasons to do this test

Low DHEA is associated with accelerated aging



Hormone Testing: My Clinical Paradigm

Insurance based practice \rightarrow Labs that are contracted innetwork when possible

Urine testing for metabolites and advanced stratification of risk for Fam Hx of BrCA - 24 hr urine vs dried urine seem to be on-par. Studies needed

Saliva for month long hormone panels (pre-menopausal women) and cortisol testing

66

Hormone Testing: Serum Hormones

Momon	Men		
Women FSH LH Estradiol Pregnenolone AMH (Fertility**) DHEA-S SHBG Prolactin Testosterone (total) Progesterone **	Men FSH LH Estradiol Pregnenolone Testosterone (total and free) DHEA-S SHBG PSA Prolactin DHT		
Progesterone ** IGF-1	IGF-1		



Urinary Hormone Testing Profiles

28 Day Salivary Hormone Testing



- Very useful when you want to look at hormones over the course of a month
- Useful for Fertility, PCOS, Luteal Phase Dysfunction, Estrogen Dominance, and Perimenopause
- Not helpful in men

Telomere Length Testing and Epigenetic Methylation Patterns





Take Home Point!

Laboratory testing is an essential part of clinical work-up.

Basic labs and Foundations of Functional Medicine may be enough to start!!

Therapeutics for Optimizing Healthspan

Interventions for Anti-Aging

Caloric Restriction (CR)

Intermittent fasting (IF), timerestricted feeding (TRF) Mitochondrial and Cellular Nutrient Support

Pharmaceutical agents: Metformin, Rapamycin

Fasting Mimicking Diet (FMD)

Optimize Hormones – HPATG Mitochondrial Supportive Food Plan (Hypothalamic-Pituitary-Adrenaland/or Mediterranean Keto Diet Thyroid- Gonadal)

Peptide therapy (Emerging)

Caloric Restriction, Intermittent Fasting, & Fasting Mimicking Diet



"Caloric restriction (CR), i.e., the reduction of caloric intake (by 10% to 40%) without causing malnutrition, has proven to be by far the most effective intervention that can extend the maximum lifespan"

Gensous N, Franceschi C, Santoro A, Milazzo M, Garagnani P, Bacalini MG. The Impact of Caloric Restriction on the Epigenetic Signatures of Aging. Int J Mol Sci. 2019;20(8):2022. Published 2019 Apr 24. doi:10.3390/ijms20082022







Stallone G, Infante B, Prisciandaro C, Grandaliano G. mTOR and Aging: An Old Fashioned Dress. International Journal of Molecular Sciences. 2019;20(11):2774. doi:10.3390/ijms20112774



Chung KW, Chung HY. The Effects of Calorie Restriction on Autophagy: Role on Aging Intervention. Nutrients. 2019;11(12):2923. doi:10.3390/nu11122923

AMPK and Insulin Resistance



Ruderman NB, Carling D, Prentki M, Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. Journal of Clinical Investigation. 2013;123(7):2764-2772. doi:10.1172/jci67227

And what does \downarrow mTOR and 1 AMPK = ???

Mechanisms Behind Caloric Restriction



Chung KW, Chung HY. The Effects of Calorie Restriction on Autophagy: Role on Aging Intervention. Nutrients. 2019;11(12):2923. doi:10.3390/nu11122923

Autophagy: The Antidote to Senescence



Stead ER, Castillo-Quan JI, Miguel VEM, et al. Agephagy – Adapting Autophagy for Health During Aging. Frontiers in Cell and Developmental Biology. 2019;7. doi:10.3389/fcell.2019.00308



Mattson MP, Arumugam TV. Hallmarks of Brain Aging: Adaptive and Pathological Modification by Metabolic States. *Cell Metab.* 2018;27(6):1176-1199. doi:10.1016/j.cmet.2018.05.011

Organ Systems affected by Caloric Restriction and Intermittent Fasting



1 Brain synaptic plasticity, neurogenesis, cognition

1 Cardiac ejection fraction, improved blood pressure

1 Insulin sensitivity, fatty acid mobilization

↓ Reduced inflammation

Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Res Rev. 2017;39:46-58. doi:10.1016/j.arr.2016.10.005



Intermittent Fasting: How to do it

Choose a window that allows for **4-8 hour of food consumption**. E.g. 12pm-6pm daily or 11am-7pm.

Do not consume any calories outside of this window

Studies demonstrate eating a "normal" diet still has benefits. I suggest a Mediterranean diet or Mediterranean Keto diet to my patients

Fasting Mimicking Diet



Fasting Mimicking Diet



Choi IY, Lee C, Longo VD. Nutrition and fasting mimicking diets in the prevention and treatment of autoimmune diseases and immunosenescence. *Mol Cell Endocrinol*. 2017;455:4-12. doi:10.1016/j.mce.2017.01.042



FMD: How to do it

Extremely well-researched, published.

5 consecutive days of pre-prepared food ~800-1100 kcal/day

Repeat 5 day FMD x 3 months

Eat "normal" diet the remainder of month

Repeat 1x quarterly to maintain benefit



Mitochondrial nutrient rich food plan may be an option

I am a big fan of the Mediterranean Keto Diet 3 weeks on/ 1 week off (Mediterranean diet still no keto)

I encourage grass-fed meats (organ meats if possible), cold-water omega 3 fatty fish, liberal use of unsaturated oils like olive, avocado, walnut, and brightly colored veggies



88

Mitochondrial and Cellular Support Nutrients

Mitochondrial and Cellular Support Nutraceuticals

NAD (NMN/NR)

Resveratrol

Pterostilbene

Berberine

Curcumin



NAD: Nicotinamide adenine dinucleotide

Sirtuin Activator

Decreases oxidative stress

Increases mitophagy

Signals for DNA repair enzymes

Produced de novo in mitochondria and nucleus under appropriate conditions



Imai SI, Guarente L. It takes two to tango: NAD* and sirtuins in aging/longevity control. NPJ Aging Mech Dis. 2016;2:16017. Published 2016 Aug 18. doi:10.1038/npjamd.2016.17

How to increase NAD with Nutraceuticals

Nicotinamide Riboside

Nicotinamide Mononucleotide

Both widely available commercially





Yoshino J, Baur JA, Imai SI. NAD⁺ Intermediates: The Biology and Therapeutic Potential of NMN and NR. Cell Metab. 2018;27(3):513-528. doi:10.1016/j.cmet.2017.11.002

"Supplementing these NAD" intermediates has shown preventive and therapeutic effects, ameliorating age-associated pathophysiologies and disease conditions"

Yoshino J, Baur JA, Imai SI. NAD⁺ Intermediates: The Biology and Therapeutic Potential of NMN and NR. *Cell Metab*. 2018;27(3):513-528. doi:10.1016/j.cmet.2017.11.002

Dosing NAD+ Precursors

Animal studies indicate doses in the thousands of milligrams would be optimal for human results (based on mice studies). *While SAFE, this would be cost prohibitive for most people*

Standard dose from most supplements is between 100mg-300mg in commercial preparations

NR or NMN Dosing: 250mg-1000mg qd - BID

Resveratrol & Pterostilbene

"Recent studies suggest that both of them are potential candidates as anti-aging agents through modulating the hallmarks of aging, including oxidative damage, inflammation, telomere attrition, cell senescence"

Resveratrol derived from grapes 🍓

Pterostilbene comes from blueberries



Dosing:

Resveratrol 250mg-500mg qd-BID

Pterostilbene 50mg-150mg qd-BID

Li YR, Li S, Lin CC. Effect of resveratrol and pterostilbene on aging and longevity. *Biofactors*. 2018;44(1):69-82. doi:10.1002/biof.1400



Li YR, Li S, Lin CC. Effect of resveratrol and pterostilbene on aging and longevity. Biofactors. 2018;44(1):69-82. doi:10.1002/biof.1400

Berberine & Curcumin: Powerful Combo

Berberine is best studied and known for its anti-diabetic properties which increase AMPK

Curcumin is a potent antiinflammatory mediator and inhibitor of NF-kB

Dosing:

Curcumin: 500-1500mg BID

Berberine: 500mg qd-TID



98



Xu Z, Feng W, Shen Q, et al. Rhizoma Coptidis and Berberine as a Natural Drug to Combat Aging and Aging-Related Diseases via Anti-Oxidation and AMPK Activation. Aging Dis. 2017;8(6):760-777. Published 2017 Dec 1. doi:10.14336/AD.2016.0620

Curcumin and Aging: Mechanisms

CR Mimicking

Increases senolytic activity

Reduces NF-kB

Inhibits mTOR

Sirtuin activator



Bielak-Zmijewska A, Grabowska W, Ciolko A, et al. The Role of Curcumin in the Modulation of Ageing. Int J Mol Sci. 2019;20(5):1239. Published 2019 Mar 12. doi:10.3390/ijms20051239

Rx: Metformin & Rapamycin

Rx: Metformin and Rapamycin

Metformin / Glucophage

 \rightarrow Most widely prescribed anti-diabetes drug in the world

Rapamycin / Sirolimus

DIRECT mTOR inhibitor

Side effects are mostly GI

Organ transplant drug

→ Depletes B12

Dosing: 500mg-1000mg qd-BID

 \rightarrow Kidney toxicity at higher doses

102



Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a Tool to Target Aging. Cell Metab. 2016;23(6):1060-1065. doi:10.1016/j.cmet.2016.05.011

Take Home Point!

Caloric restriction programs are an essential part of anti-aging and extending healthspan.

Supplements and Metformin may augment caloric restriction programs and should be strongly considered

104

My Top 3 : Anti-Aging Approach

#1 Reduce inflammation and treat insulin resistance

#2 Optimize mitochondrial function, density, and resilience

#3 Get your hormones right... Sex hormones, stress hormones, metabolic hormones... ALL OF THEM!

Hormones HPATG

HPATG: Optimization of Hormones

The HPATG axis is a closely knit orchestra of communicators that relies on the balance of each other to ensure the others are "intune"



Hypothalamus – Pituitary

Brain Hormones:

Ensure you are looking at at least LH, FSH, Prolactin in standard work-up

Hypothalamic hormones not typically tested

Refer to endo when needed.



108



Adrenal Hormones



Adrenals hormones are essential for life.

Epinephrine, norepinephrine, cortisol, mineralocorticoids

Labs:

Serum Cortisol, DHEA-S Salivary 4-point Cortisol when needed

Gonadal Sex Hormones



Manage Prior to or Concurrently

Inflammation Insulin resistance Mitochondrial dysfunction Gut Health and Detoxification

Prior to any therapeutics for sex hormones

Sex hormone work-up done concurrently or after Pituitary – Adrenal – Thyroid hormones

Women's Hormones

(HUGE topic)

Menopausal Management

Low Libido

Vaginal Dryness

Therapeutics

Men's Hormones

(Still HUGE topic, but simpler)

Andropause

Low Libido

Erectile Dysfunction

Therapeutics

112

Perimenopause and Menopause



Symptoms:

Hot flashes, irritability, sleep disturbance, excessive bleeding, weight gain, loss of libido, vaginal dryness

Average age of menopause is 52 years old

Definition of menopause is no menses for 1 year

Hormone Fluctuations during Menopause



114

Menopause Labs to Consider

Serum labs are covered under insurance, generally speaking. <u>Gives snapshot</u>.

Urine testing gives metabolites and helpful for understanding estrogen processing FSH LH Estradiol Pregnenolone DHEA-S SHBG Testosterone (total) Progesterone **



Lifestyle Approaches to Menopausal Management



✓ Increase fiber (flaxseed)

✓ Reduce (or eliminate) ETOH

✓ Exercise routinely

✓ Balance adrenals



✓ Sleep is essential

✓ Reduce caffeine

✓ Balance Blood sugar

✓ Avoid toxins (cosmetics!!)

116

Why does the GI system matter in Menopause Management?

Fat soluble hormones \rightarrow Liver \rightarrow Phase 1 & Phase 2 \rightarrow Water soluble & excretable form

IF the gut is unhealthy, liver is dysfunctional, OR excessive amts of beta glucuronidase is present

Hormones recycled back into fat soluble form!!



|↓|



My Botanical Approach to Menopause

Detoxification food plan

Siberian rhubard preparation ERr 731: 4mg qd- BID

Black Cohosh: 250mg BID

Lavender oil extract for anxiety "Silexan": 160mg qhs



Bioidentical Hormone Replacement Therapy and Menopause

✓ Bioidentical Estrogen (E2) is not the same as Premarin (horse estrogen)

✓ Bioidentical Progesterone is not the same as Medroxyprogesterone (paired with Premarin)

✓ Bioidenticals are safe, effective, and great options to consider for menopause and healthy aging



120

References for BHRT Therapy and Safety

- Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study [published correction appears in Breast Cancer Res Treat. 2008 Jan;107(2):307-8]. *Breast Cancer Res Treat*. 2008;107(1):103-111. doi:10.1007/s10549-007-9523-x
- de Lignières B, de Vathaire F, Fournier S, et al. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. Climacteric. 2002;5(4):332-340. doi:10.1080/713605312
- L'Hermite M. HRT optimization, using transdermal estradiol plus micronized progesterone, a safer HRT. Climacteric. 2013;16 Suppl 1:44-53. doi:10.3109/13697137.2013.808563
- Mueck AO. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. Climacteric. 2012;15 Suppl 1:11-17. doi:10.3109/13697137.2012.669624
- L'hermite M, Simoncini T, Fuller S, Genazzani AR. Could transdermal estradiol + progesterone be a safer postmenopausal HRT? A review. Maturitas. 2008;60(3-4):185-201. doi:10.1016/j.maturitas.2008.07.007

My BHRT Approach to Menopause

Sleep disturbance, moodiness, anxiety, irritability?

✓ Progesterone alone 25mg-50mg qhs to start

✓ DHEA if low 2.5mg-10mg q AM Low libido, vaginal dryness, hot flashes, dry skin, depression, cognitive changes?

Estradiol transdermal .025-.075mg/24 hr + Progesterone
 100mg qhs

✓ Estriol vaginal suppositories 2mg x 14 nights and then 1-2x weekly thereafter

Take Home Point!

Menopause management is combination of detox foods, sleep support, botanicals, and hormones (when appropriate)

Remember the adrenals, thyroid, and gut are essential to co-manage.

122

Women's Hormones

Men's Hormones

(HUGE topic)

Menopausal Management

Low Libido

Vaginal Dryness

Therapeutics

(Still HUGE topic, but simpler)

Andropause

Low Libido

Erectile Dysfunction

Therapeutics

124

Andropause and Hormone Deficiencies in Men

It's not always just about testosterone...

Check on thyroid, adrenal, and metabolic markers beyond just sex hormones

Check in on gut health, stress, and anxiety/ depression

Men generally do not make medical appts unless absolutely necessary



126

ADAM Questionnaire

- 1. Do you have a decrease in libido (sex drive)?
- 2. Do you have a lack of energy?
- 3. Do you have a decrease in strength and/or endurance?
- 4. Have you lost height?
- 5. Have you noticed a decreased "enjoyment of life"
- 6. Are you sad and/or grumpy?
- 7. Are your erections less strong?
- 8. Have you noticed a recent deterioration in your ability to play sports?
- 9. Are you falling asleep after dinner?
- 10. Has there been a recent deterioration in your work performance?

Causes of Low Testosterone

✔ Obesity / Metabolic syndrome/ Insulin Resistance

Endocrine disruptors – Plastic exposures, BPA, etcs

✓ Excessive ETOH consumption

- ✓ Chronic inflammation
- ✓ Chronic Opioid Use
- ✓ Hypercortisolemia



Insulin Resistance in Men with Symptoms of Androgen deficiency



Park B, Lee YJ. Upcoming Aging Society and Men's Health: Focus on Clinical Implications of Exercise and Lifestyle Modification. World J Mens Health. 2020;38(1):24-31. doi:10.5534/wjmh.180103



Laaksonen D, Niskanen L, Punnonen K, et al. Sex hormones, inflammation and the metabolic syndrome: a population based study. European Journal of Endocrinology. 2003;149(6):601-608

Goncharov NP, Katsya GV, Chagina NA, Gooren LJ. Three definitions of metabolic syndrome applied to a sample of young obese men and their relation with plasmatestosterone. The Aging Male. 2008;11(3):118-122.

Male Hormone Labs to Consider

- ✓ FSH
- 🗸 LH
- Estradiol
- ✓ Pregnenolone
- ✓ DHEA-S
- ✓ SHBG
- Testosterone (total and free)
- ✓ IGF-1✓ DHT✓ Prolactin
 - ✓ PSA
 - ✓ CBC



Lifestyle Approaches to Andropause Management



"Manly man" Botanicals for Testosterone



 \rightarrow Black seed (Nigella sativa)



Santos HO, Howell S, Teixeira FJ. Beyond tribulus (Tribulus terrestris L.): The effects of phytotherapics on testosterone, sperm and prostate parameters. J Ethnopharmacol. 2019;235:392-405. doi:10.1016/j.jep.2019.02.033

My Botanical Approach to Low T

Mediterranean Diet

Ashwaganda 1000mg BID

Fenugreek 1000mg BID

Long Jack (AKA Tongkat Ali) 600-1200mg qd

Multivitamin that includes Zinc 15mg, Vit E 200 IU, and B12

**DHEA 25-75mg as needed



134

My BHRT & Rx Approach to Andropause/ ED

 \rightarrow Low Total and Free T on two occasions in AM ?

→ Fatigue, low mood, loss of motivation, and low libido?

✓ Initiate TRT between 50mg-100mg daily with topical or IM injectable

 \rightarrow Erectile Dysfunction due to vascular dysfunction?

✓ L-Arginine 1500mg-3000mg qd

✓ PDE-5 Inhibitors like sildenafil and tadalafil if needed

Take Home Point!

Testosterone deficiency **often** does not come in isolation. Look for metabolic, adrenal, and thyroid dysfunction FIRST.

Testosterone replacement supports cardiovascular health and does not CAUSE prostate cancer but is contraindicated in active PrCA.

136

THANK YOU!!