ALZHEIMER'S TREATMENT:

PREVENTING AND REVERSING COGNITIVE DECLINE

THEORY SUMMARY & INTERVENTION DETAILS

This review was prepared on 12/8/18

The following summary is principally based on the book: *The End of Alzheimer's – the First Program to Prevent and Reverse Cognitive Decline* by Dale E. Bredesen, M.D.; Avery, NYC, 2017.

We strongly suggest that you buy this book. It is available in a variety of formats at Amazon.com.

Introduction

The following synopsis & summary may help you to find this book easier to follow. It is very much the same material just organized in a different fashion. The book provides a good deal of science and a critical mix of anecdotal cases. The author claims to have many more such cases today than when the book was written. The Protocol to prevent and reverse cognitive decline is based on Dr. Bredesen's theory about the many "causes" or contributors to cognitive decline and primarily Alzheimer's disease (AZD).

Dr. Bredesen's protocol for AZD is called "ReCODE". It has been acquired by a health care company called AHNP Health, a for-profit entity with other interests in the healthcare field. Dr. Bredesen is part of that team.

To do the Protocol correctly you will need a team of medical professionals, including a ReCODE trained (certified) practitioner in order to have access to all of the tools suggested for use by Dr. Bredesen. In order to access these practitioners you must first pay their sign-up fee. Currently there aren't a large number of certified practitioners so you may have to travel to meet with one. They are not all MDs. Since some tests and interventions require prescriptions, you will have to weigh that in consideration of the type of practitioner you want to use. Their prices for the critical first year of evaluation and treatment will vary substantially since many of the practice concierge type medicine and don't process insurance. Web links are provided for you to explore this option. A rough cost estimate is also provided near the end of this report. It isn't impossible to "do-it-yourself", if your own physician will cooperate in the testing phase. You might even find a "functional medicine "practitioner", not ReCODE certified, who will work with you on this program. However, without going through the ReCODE system, you will not have the benefit of the computer based algorithm review of you condition.

Many will not be able to afford the full ReCODE Protocol. We estimate the first years cost to range from $5,400 to $23,000, depending on how many potential contributing factors you have. Although this is a small amount relative to the actual cost of care for dementia, it is cash that many will not have. They have no formal program for assistance. With the help of the information contained herein, and with the help of willing local medical professionals, you can go a long way towards improvement on your own.

Table of Contents

A. What Causes AZD?

AZD occurs when dependence receptors that reach out for hormones, Vitamin D, brain derived neurotrophic factor (BDNF) and many other neuron and synapse supporting molecules come up empty or short. APP reacts by sending out four downsizing "memos" synapse and neuron destroying molecules, including amyloid beta (Aβ). ApoE4 increases the downsizing "memo"/ quartet snips, and suppresses the healthy "duo." ApoE4 reduces the clearance of Aβ, > more Aβ. (prionic loop).

ApoE4 also enters the nucleus and binds to DNA in the "upstream" regions (called "promotor") of any of 1,700 different genes and reduce the production of related/associated proteins. There are only 20,000 genes in the human genome. 1,700 is 8.5% of total!

This explains why ApoE4 is also involved in CVD, inflammation, and more (bad stuff):

- Shuts down gene making SirT1 (linked to longevity and has an anti-A20 effect. (Resveratrol activates SirT1)
- Associated with activation of NF-KB (nuclear factor Kappa B) which promotes inflammation.

Where does AZD come from and when does it start?

1. It is a protective response to inflammatory insults…

    a. inflammatory insults
    b. Suboptimum nutrients
    c. Trophic factors
    d. Hormone levels
    e. Toxic compounds

    This results in the APP reception to be cut into a quartet including AB/ destroys synapses and neurons.

2. AZD is a state of the brain in which there is an imbalance between the reorganization of existing and new synapses that have outlived their usefulness (healthy destruction) and the maintenance or creation of existing and new synapses respectively, which the brain needs to sustain old memories and form new ones. Too much "quartet" and not enough "duo."

3. How to give yourself AZD: Live in a way that keeps your brain supplied with as many possible of the 36 factors that influence whether APP gets cut into the "quartet"

4. How to prevent it? Minimize the "36 factors" covered later.

5. 99% of the AZD trials have failed - they target only 1 of the 36 issues/contributors.

6. How to stop AZD if it has already begun? Test for status of each end optimize.

7. How to stop AZD if it has already taken hold? Evaluate status (genetic, biochemical) and addon each.

B. GENETICS

1. Primary AZD gene:

    a. APOE (apolipoprotein E; apolipoprotein is a protein that carries lipids - i.e. fats)

    b. Other genes: Presnilin-1 (PS1) and Presenilin-2 (PS2) increase risk of AZD before age 60 (5% of AZD cases)

2. Gene variant (Allele)

    a. APOE4 (About 75 million in USA). The strongest genetic risk for AZD; Original form of APOE.
    b. 1 copy + 30% risk increase
    c. 2 copies + 50% to 90% risk increase
    d. 0 copies 9% risk
    e. 1 in 9 (USA) >= 65-year olds get AZD with or without APOE4.
    f. Globally 160 million by 2050 will develop AZD.

3. Brain Neurons

    - 100 billion
    - Each with 10,000 connections (synapses)
    - Quadrillion (1×10^{15}) total synapses (connections)

4. Gene p75NTR common neurotrophin (Ligands) receptor

    Neurotrophin ligands support cell health (vs. death). When the ligand is present in the p75NTR receptor, cell suicide prevented. Without the ligand, then programmed all death.

    Therefore: Once the cell produces this receptor, it is dependent on the ligand for survival- the neurotrophins "key" must stay in the "receptor" on the neuron dies (called "dependence receptors".)

    21 dependence receptors have been identified controlling various molecules from trophic factor, to hormones, to anchoring molecules (hold cells in place) control cancer spread (metastasis), embryo development, nervous system targets, cell shrinkage, etc.

    Neurotrophins, when absent, cause dependence receptors to tell their neurons to die. If something blocks the receptors from the ligand, they also die.

    That "thing" which blocks the ligands from the receptor cells is the peptide amyloid-beta (Aβ) Normal function of Aβ not clear.

    Neurons and cells may normally die, (damaged, can't do its job, etc.) to make room for replacements.

    In AZD, Aβ causes neurons to die faster than the normal rate of replacement.

    Aβ comes from the amyloid precursor protein (APP). APP is also a dependence receptor and can occur near nerve synapse. (APP has 695 amino acids with Aβ being 40-42 of those 695 amino acids).

    Neurons produce APP protease cuts @ 1 spot or 3 spots

    - β site
    - Gamma (γ) site
    - Caspase site
        1. 1 cut = 2 Anti AZD fragments (peptides) [Soluble APP*alpha*1 & *alpha* CTF]
           -or-
        2. 3 cuts = 4 Pro AZD fragments [Soluble APPβ, Jcasp, C31, Aβ]

C. RECODE FOUNDATION BASICS

Want to Maximize "Duo" cuts - Synaptoblastic

a. 1 cut = 2 peptides
    i. Soluble APP*alpha*1
    ii. *Alpha* CTF (inside cell membrane)
b. Maintain synaptic connection
c. Nourish neuron "fingers"
d. Block neuron suicide

Want to Minimize "Quartet" cut - Synaptoclastic

a. 3 cut = 4 peptides
    i. Soluble APPβ
    ii. Jcasp
    iii. C31
    iv. Aβ

b. Loss of brain synapses
c. Part of neuron is shrivelled up (connectors/ dendrites)
d. Activation of neuron suicide program

Physiological imbalance (like in above APP) also occurs in Osteoporosis:

a. Bone formation - by osteoblasts
b. Bone resorption - by osteoclasts

Cancer

a. Oncogene – cytoblastic
b. Tumor suppressor – cytoclastic

APP & AZD

If APP "grabs" a molecule called NETRIN -1 = DUO

If APP "grabs" Aβ = QUARTET (which produces more Aβ)

Therefore: you need Aβ to make more Aβ – where does it start?

By removing trophic support (like Netrin-1) APP produces Aβ. This is called a "Prionic" loop.

Aβ bites the APP receptor and creates another Aβ

These prionic loops continue & produce more synapse & neuron destroying Aβ.

ReCODE is designed to shift the APP balance back to Duo from Quartet.

1. SUMMARY A

APP can promote neurite growth & synaptic maintenance

Therefore: support formation & maintenance of memories

DUO: When NETRIN-1 binds APP = outgrowth occurs

QUARTET: When Aβ peptide binds APP – retraction occurs

2. SUMMARY B

Neurons sport receptors called APP (amyloid precursor protein)

Netrin-1:

APP grabs NETRIN-1 (floating by in the INTERCELLULAR environment) signal keeps all (neuron) healthy

Ø:

APP fails to grab NETRIN-1 and lacks other trophic support, it defaults to signal telling the neuron to commit suicide

Aβ:

APP grabs Aβ, biochemical cascade reactions cause APP to cut into quartet, releasing more Aβ. Aβ begin to outnumber the NETRIN-1 & more Aβ produced. More neurons die.

3. OTHER

All act at the crux of the AZD pathway: OTHER APP molecules (keys). All are linked to AZD Good & Bad.

- Estrogen
- Testosterone
- Thyroid hormone
- Insulin
- Inflammatory molecule NF-KB
- Longevity molecule sirtuin SirT1
  (Activated by resveratrol – a.k.a. found in red wine)
- Vitamin D
- Sleep
- Stress
- Many others

Synapse building is synapse dismantling are in dynamic equilibrium in young brains. We retain needed info and jettison the rest (broken up for parts, to be recycled into synapses encoding more important memories.

As we age, trophic support diminishes (hormones, nutrients, more...) Receptors inform APP that the brain needs downsizing since it can't support what it has due to factors previously discussed. The brain is pulling back support for non-life sustaining function.

4. 36 HOLES IN THE ROOF

36 contributors to whether APP takes the "duo" path (AZD preventing) or "quartet" path (AZD causing) will be the focus of the rest of this review.

D. **5 KEY DRIVERS OF COGNITIVE DECLINE**

1. Insulin resistance
2. Inflammation/infections
3. Hormone, nutrient, & trophic factor optimization
4. Toxins (chemical, biological, physical)
5. Restoration & protection or lost/dysfunctional synapses

E. **TERMINOLOGY & OTHER DEMENTIA**

DEMENTIA Cognitive decline w/cost of many metal abilities. Memory loss is early sign (reading, writing, speaking, following a conversation, reasoning, calculating, organizing, and planning)

CAUSES Many causes. ReCODE works on AZD, MCI, and SCI but don't know about the others

- AZD

  Most common. Marked by amyloid plaques & neurofibrillary tangles, but likely not caused by them.

  PET (position – emission tomography) & CSF analysis can ID presence.

  Generally diagnosed based on symptoms

  Always fatal under current standard of care

- VASCULAR DEMENTIA

  Caused by reduced blood flow to brain & marked by multiple strokes.

  AZD & VD overlap in some areas.

- FRONTOTEMPORAL DEMENTIA

  Features changes in behaviour, memory problems, and difficulty speaking

- LEWY BODY DEMENTIA

  Fairly common (AZD is 5x more common); visual hallucinations, delusions, increased sleeping, flinging of limbs during sleep called REM behavioural disturbance.

- SCI – Subjective Cognitive Impairment

  Worsening cognition that is noticeable to the individual but falls within normal range when tested (normal may be a decline for a highly intelligent person)

  PET & CSR often abnormal at early stages.

  MRI may show some shrinkage of brain regions.

  Often lasts decade or more before progressing to MCI.

- MCI – Mild Cognitive Impairment. Follows SCI. Neuropsychological testing shows abnormal memory, organizing, speaking, calculating, planning, etc.Still able to perform activities of daily living (cut, both, dress).

  Does not always progress to AZD.

F. **TYPES OF AZD**

1. Inflammation ("Hot") – responds most quickly to ReCODE protocol

a. Primarily anything causing brain inflammation

- Neuroinflammation: Trauma, infection, toxic metabolites, some proteins
- Toxins
- Leaky gut or leaks, blood/brain barrier
- Insulin Resistance
- Fatty acid imbalance (omegas)
- Diet high in lectins
- "AGES" (advanced glycation end products – protein & lipids that become glycated as a result of exposure to sugars)
- APOE 4 - 25% of us population (75 mil) 30% risk of AZP - 50-60
    - APOE 3/3 most common – 9% chance of AZD - 60-70
    - APOE 4/4 (7 mil US) > 50% risk of AZD - Age: 40-50

Type 1 is most common in people w/APOE4/4 or 4/x

b. Biochemical Markers

1. Increase in C-Reactive Protein (made by liver in reaction to infections & other inflammatory issues)
2. decreases in albumin/globulin ratio

   Albumin is a "trash collector" in the blood, removing toxins including Aβ. Globulin is a catchall name for 60 blood proteins including antibodies. Ratio decreases with inflammation.
3. Increase in Interleukin – 6, which rises with inflammation
4. Increase in tumor necrosis factor (another protein whose level rises with inflammation)
5. Metabolic & hormonal abnormalities such as insulin resistance
6. Homocysteine may be too high

1.5 Glycotoxic (AZD1 / inflammation + AZD 2 trophic loss)

a. Imbalance of glucose/insulin usage in the brain

- Pancreas = insulin degrading enzyme (IDE)

  Breaks down insulin & amyloid beta (Aβ)

- If IDE used up by insulin excess (because of diet too high in sugar), none available to eliminate amyloid-β

b. Insulin Resistance! Glucose is chronically high, resulting in:

- Glycation (alterations in various proteins) and in inflammation
- High insulin from high glucose = insulin no longer works as well as a neurotrophic support molecule = loss of trophic support as in type 2

2.0 **Metabolic** / Trophins Lost (**Atrophic – "cold"**) Responds more slowly to ReCODE

a. Imbalance in endocrine system (hormones)

b. Nutrient depletion

c. Neurotrophic loss (brain cell depletion exceeding replacement)

d. Causes/contributors to Type 2 ("cold")

- APOE 4 (most common – Type 2.0 – in people APOE 4/4)
- Hormone imbalances
  - Vitamin D, steroids (sex & neuro), Thyroid, adrenal, estrogen, progesterone, testosterone, pregnenolone are suboptimal
- Insulin resistance
- Methylation issues
- Mitochondrial damage
- Neurotrophic loss (brain atrophy)
- Nutrient depletion
- Homocysteine may be high (ditto for Type 1.0)

e. No evidence of inflammation: markers of inflammation may be lower than normal. Brain synapse support has "dried up."

2.5 <u>Type 1.0 (hot) + Type 2.0(cold)</u> (occur together sometimes)

a. Inflammation or T 1.0 w/reduced support for brain synapses like in T2.0

b. One variant of T 1.0 + T 2.0 is so common it deserves its own name:

- <u>Type 1.5 Glycotoxic ("sweet")</u>

c. T1.0 + T2.0 or T 1.0 & T 2.0 individually are all the result of the "downsizing" program in which there is an imbalance between the production & destruction of synapses.

Note: Type 3.0 is very different

3.0 **<u>Type 3 -Toxins</u> (aka Inhalation Type)** ("**Toxic**"/ "Vile")

Note: In T3, removal of Aβ may not be good thing.

a. Toxic/infectious – Environmental

Causes/Contributors:

- APOE 3 (most common allele) – Not APOE 4
- Heavy metals
    a. Hg amalgams
- Hormonal Imbalances
- HPA – Axis Imbalance
- Infections
    a. Mold, lyme, active EBC
    b. Oral, nasal, gut dysbiosis
- Low zinc/high copper ratio
- Toxins
    a. Haptens, pesticides, NSAIDS, PPIs, statins, other drugs
- Psychiatric disorders (some correlation)

b. Does not typically run in families (APOE3 – Not 4) and if a relative had it they were typically 80+ y/o.

c. T 3.0 typically strikes younger (symptoms in late 40's to early 60's, often following great stress rather than beginning as memory loss.)

d. Often starts w/cognitive difficulties involving numbers, or speech or organizing

e. Loss or all memories (new & old + procedural memories)

f. May not be diagnoses as AZD (MRI + & PET scans can show)

g. Biomarkers of Type 3.0

1. Brain scan / impacts

   Other types may show focus on hippocampus

   This is all over atrophy (shrinkage)

2. Often there is neuroinflammation and vascular leaks

   MRI flair – fluid attenuated inversion recovery will show multiple abnormal white spots

3. Often low Zinc (Zn) in blood, high in Copper (Cu), high ration of Cn/Zn

   Ratios s/b = 1.0 with 100 mcg/dL each

   Frequently this subtype has Zn = 50, Cu = 170 (ratio 3.4)

4. Often 1st diagnosis is frontotemporal dementia or depression. Not diagnosed properly until PET scan and/or spinal fluid indications

   - CSF - reduction in Aβ42
     Increase in total tau
     Increase in phospho tau

5. Hormonal Abnormalities

   Stress producing organs are dysfunctional:
   Hypothalamus, Pituitary, Adrenal glands (HPA Axis)

   Labs show:

   - Low cortisol
   - High reverse T3
   - Low free T3
   - Low pregnenolone
   - Low testosterone
   - Other hormonal abnormalities

6. High blood levels of toxic chemicals such as:

   - Mercury (Hg) Blood test not indicative of presence or absence
     Mycotoxins (aflatoxin, ochratoxin, gliotoxin, trichothecenes)
     "DEMEMTOGENS"

   - Chelating agent needed to pull Hg out of tissues to test urine over 6 hours often chelation will show results

   - Hg amalgam fillings (50% Hg and 15% tin and silver) when properly removed, seem to improve AZD symptoms.

h. Characteristics of Type 3.0 (Toxic)

- Symptoms before 65 years old (late 40's to early 50's)
- Usually APOE4 negative (Type APOE 3/3)
- No family history (few have APOE4)
- Symptoms occur often at menopause or andropause
- Depression precedes or accompanies cognitive decline
- Headache is an early symptom - may be 1st
- Memory is not 1st or dominant problem

  Typical -
  - exec function deficits
  - Inability to manipulate numbers
  - Trouble speaking or loss of speech
  - Visual reception problems
  - Learned program (like dressing) problems
  - Precipitated by or exacerbated by stress and/or sleep loss

- Exposure to mycotoxins
- Exposure to metals (Hg, etc.)
- CIRS diagnosis (chronic inflammatory response syndrome)
  Extreme exhaustion, Weakness, Cognitive difficulties

Editor's note:
www.drelenaklimensio.com re: cirs (functional med. doc in NYC)
Cirs - umbrella term for symptom with various causes:
Causes: Tick borne illness (i.e. lyme), Mold

Best known "name" for CIRS data is Dr. Ritchie Shoemaker (Shoemaker Protocol)

- Unusual brain imaging for AZD
- FDG - PET may show frontal as well as temporoparietal reduction in glucose utilization

  MRI - generalized shrinkage in cerebral cortex and cerebellum, especially with mild FLAIR hyperintensity

- Low serum – zinc (<75 mcg/dL) or RBC Zinc
- Cu / Zn > 1.3 (should be = 1; greater than 1.3associated with cognitive decline
- HPA axis dysfunction
  - Low pregnenolone
  - Low DHEA - S
  - Low AM cortisol

- High serum

  - C4a
  - TGF – β1
  - MMP9

- Low serum MSH (melanocyte - stimulating hormone)

- HLA - DR/DQ associated with multiple biotoxin sensitivities or pathogen specific sensitivity. This is a genetic test that indicates that you are particularly sensitive to biotoxins. Present in about 25% of people.

G. Key ReCODE Treatment Concepts

1. For each abnormality, go beyond "normal levels and optimize
2. Address as many abnormalities as possible, not just one
3. For each, goal is to address root cause
4. ReCODE is personalized, based on lab values found abnormal
5. There is a "threshold" effect, like other chronic illness such as osteoporosis, cancer, and CVD must reach tipping point from synapse destruction to synapse maintenance and preservation (typically this is s/b sufficient)
6. Program is iterative
   - Phases must be tweaked to optimize guided by ongoing results
7. Drugs are dessert, not the entree
   - Drugs can be used, but not the treatment focus
8. The earlier you start, greater chance for complete reversal
9. For every element of ReCODE there is a work-around or crutch if you need it

H. Single / Monotherapy Drug

a. A single drug for AZD would have to do the following in order to maintain brain health, reverse cognitive decline, preserve synapses, and resteer the brain if already headed down the AZD path:

<u>< (reduce) > (increase) P (prevent) E (enhance) I (improve) O (optimize) A (activate)</u>

<	APP β - Cleavage
<	gamma - Cleavage
>	alpha - Cleavage
<	caspase - 6 cleavage
<	caspase - 3 cleavage
P	Aβ oligomerization
>	neprilysin
>	IDE (insulin degrading enzyme)
>	microglial clearance of AB
>	Autophagy
>	BDNF (brain derived neuroprotective protein)
>	NGF (nerve growth factor)
>	Netrin-1
>	ADNP (activity - dependent neuroprotective protein)
>	VIP (vasoactive intestinal peptide)
<	Homocysteine
>	PPZA (protein phosphate ZA) activity
<	Phospho - tau
>	Phagocytosis index
>	Insulin sensitivity
E	Leptin sensitivity
I	improve axoplasmic transport
E	mitochondrial function and biogenesis
<	oxidative damage and optimize ROS (reactive oxygen species production)
E	cholinergic neurotransmission
>	synaptoblastic signaling
<	synaptoclastic signaling
I	LTP (long term potentiation)
O	Estradiol
O	progesterone
O	EZ:P (estradiol to progesterone) ratio
O	free T3
O	free T4
O	TSH (thyroid stimulating hormone)
O	pregnenolone
O	testosterone
O	cortisol
O	DHEA (dehydroepiandrosterone)
O	Insulin secretion and signaling
A	PPAR - gamma (peroxisome proliferator - activated receptor gamma)
<	inflammation
>	resolvins
E	detoxification
I	vascularization
>	CAMP (cyclic adenosine monophosphate)

> glutathione
provide synaptic components
O All metals
> GABA (gamma - aminobutyric acid)
> Vit D signaling
> SirT1 (silent information regulator T1)
< NF - Kβ (nuclear factor kappa betta - light- chain of activated B cells)
> telomere lengthy
< glial scarring
E stem cell mediated brain repair

I. **Factors Driving Cognitive Decline - SCI, MCI, AZD**

1. **<u>Homocysteine</u>**

a. "Normal" serum 12 micromoles / L. In reality, this is suboptimal s/b 6 µmol /L or lower

If homocysteine > 6 micromoles / L lower it by taking vit B6, B12, and folate

One study showed:

- **20 mg B6**
- **0.5 Mg B12**
- **0.8 Mg folate**

Best to take **"activated" forms** of these vitamins since many have biochemistries that fail to turn the vitamins we ingest to their active forms.

Therefore: Take:

- **Pyridoxal - 5 - phosphate (PSP) form of vit B6 20 - 50 mg per day**
- **Methylcobalamin (methyl-B12) and adenosylcobalamin forms of B12 a mg per day**
- **Methyltetrahydrofolate (methyl - folate) form of folate starting with out 0.8 mg (up to 5mg) per day**

b. Recheck after 3 months to confirm 6 micromoles or < homocysteine. If not, add <u>500 mg daily of glycine betaine (aka trimethylglycine in capsule form)</u>

c. Recheck in another 3 months, if high, <u>reduce dietary methionine</u> (the amino acid from which the body makes homocysteine) by limiting consumption of: Nuts, Beef, Lamb, Cheese, Turkey, Pork, Fish, Shellfish, Soy, Eggs, Dairy, and Beans. (Dairy = cow, sheep, goats)

d. <u>VIT B6, B12, and Folate</u>

Required to keep homocysteine low. Use "active" forms

- **B6 - pyridoxal - s - phosphate (PSP)**
- **B12 - methlycobalamin**
- **B6 - Methylfolate**

e. Tests

- B12 "norm" 200-900 (suboptimal) picogram (pg/ml)

  200-350 may be deficient and related to anemia and dementia
  Goal: 500 -1,500 pg/ml

- MMA Methylmalonic acid (test maybe ordered instead of B12)

  As B12 declines, MMA increase (high MMA = low B12)
  Never get this test done alone as it can vary widely.

- Folate "norm" is 2-20 ng/ml

  aim for 10-25 ng/ml

- B6 Low end 30-50 / high end up to 110 nmol / L
  (PSP)→ Target 60-100 nmol / L
  > 110 nmol/L toxic to some peripheral nerves

2. **INSULIN RESISTANCE** (Single most important metabolic contributor to AZD)

   a. If fasting insulin > 4.5 milli-international units/L
   Hemoglobin Alc > 5.5%
   Fasting glucose > 93 mg/dL

   Therefore: Likely have insulin resistance

   Many become IR from diets high in carbs such as sugar, processed foods w/HFCS (high fructose corn syrup), sedentary lifestyles, and stressful jobs & home lives.

   b. How to combat: <See 2A + 2B + 2C>
   - DESS (diet, exercise, sleep & stress reduction)

3. **DIET KETOFLEX 12/3** (as metabolism so goes cognition)

a. KETOSIS

Ketone bodies (acetoacetate, beta-hydroxybutyrate, and acetone) produced by breaking down fat. This occurs when body runs low on carbohydrates, bodies' first source of energy)

Mild ketosis is optimal for cognitive function. Beta hydroxybutyrate increases production of the important neuron and synapse supporting molecule BDNF (Brain Derived Neurotrophic Factor) among other effects.

To promote ketosis, combine low car diet with moderate exercise (at least 150 mins/week of brisk walking or something more vigorous). AND FASTING for at least 12 hours.

Consume fats such as MCT oil or unsaturated fats such as olive oil, avocado, nuts, etc. Also promotes ketosis.

b. INSULIN RESISTANCE (IR)

- Body cannot process more than N/5g/day of sugar
  (A soft drink has 40-100g

  Foods with high glycemic index (starchy foods like bread, white rice, white potatoes, pastry, etc.) trigger insulin response

  At high levels, glucose is toxic

Editor's Note: *Table sugar (sucrose) is N 50/50 glucose/fructose. The only organ that can process fructose is liver, so it is very toxic (esp. bad is HRCS)*

Overproduction of Insulin harms cells by becoming insensitive to all that insulin (continuous).

IR contributes to T2 diabetes, fatty liver, metabolic syndrome, and AZD.

Editor's Note: *Metabolic Syndrome (METS) a.k.a. Syndrome X*

2005 National Cholesterol Education Program (NCEP)
Adult Treatment Program III (ATPIII) Define METS as having 3 of the following 5 conditions:

1. *Abdominal obesity by waist circumference*

   MEN > 40"
   WOMEN > 35"

2. *Low HDL*
   MEN < 40 mg/dl
   WOMEN < 50 mg/dl
   Anyone on meds for cholesterol

3. *High Triglycerides > 150 mg/dl -or- if on meds*

4. *High B.P. > 130 mmHg systolic | > 85 mmHg diastolic – or if on meds*

5. *Fasting blood glucose > 100 mg/dl or on meds*

1/3 of us adult population qualifies

Greater risk of CVD by 300%

Greater risk of stroke, cancer, OSA, PCOS, NASH

AZD Link w/IR:

Insulin (Ins) signaling is one of most important signals for support of neuron survival.

- Ins Binds to Ins receptor & triggers signaling that supports neuronal survival. This is blunted by chronically high ins. Levels.

- Body degrades Ins. After its job is done using enzymes. The principal one being Ins degrading enzyme (IDE). IDE also degrades Aβ. If it is busy w/ins, it isn't degrading Aβ, contributing to AZD.

2. ADDITIONALLY – "AGE"

Glucose attaches to proteins interfering with functioning. The hitchhiking glucose molecules undergo biochemical reactions to produce advanced glycation end products (AGE)

AGE:

- Cause body to think the attached proteins are foreign & you may develop antibodies triggering inflammation.

- Age receptor is "RAGE" (Reception for AGE) which also triggers inflammation

- AGE causes free radicals to form, damaging DNA and cell membranes
- Altered proteins damage blood vessels & reduce nutritional support
- Causes leaky blood/brain barrier

TARGETS

Fasting Insulin s/b 4.5 or less	micro IU/ml
Fasting Glucose s/b 90 or lower	mg/dl
Hemoglobin AIC s/b	< 5.6%

3. FIX INSULIN RESISTANCE/SENSITIVITY/GLUCOSE CONTROL
(High insulin & high glucose are 2 of most important AZD risk factors)

- Ins sens is affected by Zn. If < 100, try 20 mg to 50 mg of Zinc Picolinate daily. Recheck glucose after 2 months.
- High hemoglobin AIC (poor glucose control). Affected by low Mg. If your RBC mg < 5.2, try magnesium glycinate (500 mg/day) or magnesium threonate (2g/day)
- Cinnamon helps glycemic control. ¼ tsp/day (on food or 1g capsule). Improves lipid profile in people with T2 diabetes.
- Alpha – Lipoic Acid is an antioxidant. 60-100 mg daily
- Chromium Picolinate lowers blood glucose. 400 micrograms to 1 milligram daily
- Berberine lowers blood glucose. 300-500 mg 3x/day
- Rx to reduce blood glucose is METFORMIN

Shifting from carb metabolism to fat burning may have carb cravings and lethargy. To lower take MCT (medium chain triglycerides) oil:

Capsule – 1g

Liquid – 1 tsp

Alternative to MCT oil, use coconut oil (solid)

1 tsp to 1 tblspn – 3x/day

(Too fast = diarrhea)

Both may have drawbacks for ApoE4 positive individuals. (Use only temporary until natural ketosis established)

Use ketone meter. Target range 0.5 mm – 4.0 mm/dl

c. "FLEXITARIAN" DIET

Largely a plant-based diet with emphasis on vegetables.

Some risk, poultry and meat are ok, but treat as a condiment

- 1g of protein for each kilogram of weight / day

  Exp: 70 kg (154 lbs.) = 70 g of Protein

  3oz fish = 20g protein
  10.5oz fish = 70g protein

  1oz chicken thigh = 5.6 g protein
  12.5oz chicken thigh = 70g protein

  1oz steak = 7.8 g protein
  9oz steak = 70g protein

! IF EAT >1g/kg or protein, biochemically there is some conversion to carbohydrate.

d. 12/3 FASTING TIMES

Fasting induces ketosis & improved insulin sensitivity

12 = 12 hours between end of dinner and the next day's first meal or snack

APOE4 – should aim for 14-16 hours fast

3 = Minimum time between end of dinner and bedtime

Keeps insulin level from spiking before bedtime which can contribute not only to I.R. but inhibition to melatonin and growth hormone which aid in sleep & immune function as well as repair

Fasting 12-16 hours promotes autophagy (cells recycle components and destroy damaged proteins & mitochondria)

Fasting depletes the liver's stores of glycogen (storage form of glucose) & this helps push you into ketosis

Fasting induces ketosis

Breakfast with water (no ice) & lemon as detoxifying drink (lemon stimulates your liver and provides vitamin C)

e KETOFLEX 12/3 Helps Prevent Gut Leak & Optimize Microbiome

Also, need to avoid gluten, dairy, and other foods to which you are sensitive and may contribute to leaky gut and thus cause inflammation.

Once gut is healed, optimize microbiome using probiotics and prebiotics.

f. KETOFLEX 12/3 DIET SPECIFICS

1. Bulk of diet s/b foods w/glycemic index < 35 to keep insulin release low.

   Glycemic Index help:

   https://www.health.harvard.edu/diseases-andconditions/glycemic-index-and-glycemic-load-for-100-foods

   Organic Vegetables:

   Organic, seasonal, local & non-GMO "dirty dozen & clean 15" is a site to guide selection. https://www.elizabethrider.com/dirty-dozen-clean-15/

2. Avoid fruit juices in favor of whole fruits – Less sugar & more fiber

   Best fruits with low glycemic index include:

   - Colorful berries
   - Lemons
   - Limes
   - Tomatoes
   - Avocados

   Avoid tropical fruits as they may have high glycemic index

3. Avoid triad of foods meeting these criteria:

   - Simple carbs
   - Saturated fats
   - Lack of fiber

   Lack of fiber contributes to higher absorption of carbs (triggering inflammation and raising insulin levels)

   Fiber reduces blood sugar by reducing carb absorption and optimizing microbiome.

   Saturated fat + carbs + no fiber = IR, CVD, DEMENTIA.

4. AVOID GLUTEN & DAIRY

   Although only 5% of U.S. population has marked gluten sensitivity (i.e., celiac disease) Gluten can damage gut lining in most of us, leading to leaky gut & chronic inflammation.

   Dairy – Also causes inflammation

   Don't choose rice flour or other high glycemic index ingredients

5. REDUCE TOXINS by eating specific detoxifying plants.

Toxins – Heavy metals, endocrine-disrupting agent like BpA (bisphenol A) to biotoxins like trichothecene genes.

Certain edible plants use multiple mechanisms to sequester and eliminate toxins from our bodies via urine, sweat, and stool. Those plants include:

- Cilantro
- Cruciferous veggies
    - Cauliflower
    - Broccoli
    - Cabbage
    - Kale
    - Radishes
    - Brussel Sprouts
    - Turnips
    - Watercress
    - Kohlrabi
    - Rutabaga
    - Arugula
    - Horseradish
    - Maca
    - Rapini
    - Daicon
    - Wasabi
    - Bok Choy
- Avocado
- Artichoke
- Beets
- Dandelions
- Garlic
- Ginger
- Grapefruit
- Lemons
- Olive Oil
- Seaweed

6. INCLUDE GOOD FATS (Avocados, nuts, seeds, olive oil, MCT oil)

Re: ApoE4 (special case) – see https://www.apoe4.info

If you have the ApoE4 allele do this:

Use MCT oil to restore insulin sensitivity. Since MCT is saturated fat (on the eat-less list), after restoring ins sens., switch over to polyunsaturated fatty acids (olive oil, other cold pressure oils) or monounsaturated fatty acids such as in nuts.

7. Avoid processed foods in favor of whole foods (organic)

Avoid toxins.

8. FISH ARE OPTIONAL

- Good Omega-3 fat source
- Some have high Hg & other toxins
- Avoid large mouth, long lived species.
  (Shark, swordfish, tuna – all high in Hg)
- Favor SMASH fish (salmon, mackerel, anchovies, sardines, and herring)
- Wild caught (us farmed) offer better omega-3 to omega-6 ratios and have fewer toxins.

9. MEAT IS A CONDIMENT, not the main course.

Daily protein requirement (1g Protein / 1 kg weight is plenty)
(1lb – 0.454 kg; 170 lb. man = 77 kg = 77 g protein
130 lb. man = 59 kg = 59 g protein / day)

MEN = 50-70 g/day
WOMEN = 40-60 g/day

More than 1g/kg, contributes to carbohydrate (CH) burden via a process called Transamination (protein to carb conversion)

Also get protein from beans, soy, eggs & nuts.

Buy meat that is Organic. Omega 3/6 ratio is better.

- Grass fed beef
- Pasture raised chicken
- Eggs from same.

10. Include Probiotics (bacteria) and Prebiotics (food)

Dietary sources are best.

Probiotics *(Lactobacillus & Bifidobacterium*)

Fermented foods:

- Kimchi
- Sauerkraut
- Sour pickles
- Miso soup
- Kombucha
- Not yogurt – dairy & too much sugar

Yeast:

Saccharomyces boulardi capsule (good, esp. if have diarrhea)

Fights *Candida*

After antibiotic use, probiotics are important.

Prebiotics

Choose food to support the good probiotics.

Avoid foods for bad bacteria (Firmicutes – *Bacillus, Clostridia*, gram positive species, mycobacterium, and many others) as these bacteria are related or linked to diabetes, IBS, metabolic syndrome.

FOODS:

- Jicama
- Onions
- Garlic
- Raw leek
- Raw Jerusalem artichokes
- Dandelion greens.

11. DIGESTIVE ENZYMES ARE HELPFUL

If acid reflux, acute inflammation, chronic stress, reduced stomach acid or older than 50

May help to take digestive enzymes with meals

Also help in switching from CH diet to good fat rich diet

12. OPTIMIZE NUTRITION & COGNITIVE PROTECTION WITH SUPPLEMENTS

Unless lab values are optimal, take these:

a. Vitamin B – 50mg (memory formation)

VITAMIN B (Thiamine)

- Deficiency associated with alcohol abuse & malnutrition associated memory loss (Wernicke – Korsakoft Syndrome)
- Levels can drop from eating foods containing thiamine – degrading enzymes, such as tea, coffee, alcohol, & raw fish (rare cause)
- Test by measuring thiamine pyrophosphate (TPP) in RBC

GOAL

Thiamine (serum) = 20-30 n mol/L

-or-

TPP (RBC) = 100-150 ng/ml

b. Pantothenic Acid – 100 – 200 mg (focus/alertness)
c. B_6 / B_{12} / Folate combo if homocysteine > 6.0
d. Vitamin C – 1g if C suboptimal or Cu/Zn > 1:2
e. Vitamin D – (Note see Vit D_3 discussion noted elsewhere)
    - 2500 IU/day until serum levels reach 50 to 80

f. Vitamin E (as mixed tocopherols & tocotrienols) 400 – 800 IU
    - For those w/VIT E < 13.0
    - VITAMIN E (set of compounds – tocopherols, tocotrienols…)
    - Antioxidant
    - Anti AZD effect
    - Interact w/fatty cell membrane protecting them from damage by scavenging free radicals
    - One of very few monotherapies for AZD that has shown to slow Cog. Decline (modestly)
    - GOAL
      Vitamin E = 12 – 20 mcg/ml (alpha – tocopherol)

g. Vitamin K_2 as MK7 100 mcg, for those taking Vitamin D
h. Resveratrol – 100 mg for all
i. Nicotinamide Riboside – 100 mg for all
j. Citicoline – 250 mg @ 2x/day (supports synaptic growth & maintenance)
k. Alcar (acetyl – L – carnitine) – 500 mg (to increase nerve growth factor, especially for those with contributors of Type 2 AZD.)
l. Ubiquinol – 100 mg (support mitochondrial function)
m. Polyquinoline Quinone (PQQ) 10-20 mg (mitochondrial support)
n. Omega-3 fatty acids
o. Whole coffee fruit extract (WCFE) – 100 mg 1x or 2x / day for 3 months, then withdraw slowly over one month (increases BDNF & is especially important for those with T2 AZD)
p. SPECIFIC HERBS SUPPORT SYNAPTIC FUNCTION
    - ASHWAGANDHA - 500 mg 2x/day with meals
      (Reduction of amyloid & help with stress)

    - BACOPA MONNIELI – 250 mg 2x/day with meals
      (Improves cholinergic function, one of brains key neurotransmitter systems)

    - GOTU KOLA – 500 mg 2x/day with meals
      (Focus & alertness)

    - HERICIUM ERINACEUS (LION'S MANE) – 500 mg 1 or 2x/day
      (Inc. nerve growth factor, especially for T2 AZD)

    - RHODIOLA – 200 mg 1 or 2x/day
      (Anxiety & stress)

    - SHANKHPUSHPI (SKULLCAP) 2-3 TSP / DAY (2 caps)
      (Enhance branching of neurons in the hippocampus)

    - For those with T3 (toxic) AZD, MCI or SCI

        - TINOSPORA CORDIOLIA (guduchi) to boost immune support
          300 mg with meals, 2 or 3x/day

        - GUGGUL (removes toxins in the gut, like charcoal)

    300 mg or 750 mg/day as capsules of guggul extract

- For those with T1 AZD, MCI, or SCI or w/bowl symptoms

    - TRIPHALA (amalaki + haritaki + bibhitaki)

To reduce inflammation. Take on empty stomach (capsule or tea)

13. AVOID DAMAGING FOOD WHILE COOKING

Minimize loss of nutrients and the production of AGE's (advanced glycation end products).

AGE's are glycotoxins created by a rxn between sugars and proteins or lipids.

High levels create oxidative stress, inflammation, and pathologies seen with diabetes & chronic disease.

G. Food List

1. Foods to Eat Frequently

- Mushrooms
- Cruciferous vegetables
- Leafy green vegetables
- Wild caught fish, especially "smash" fish
- Pasteurized eggs
- Resistant starches such as sweet potatoes, rutabagas, parsnips, & green bananas
- Probiotic foods such as sauerkraut & kimchi
- Prebiotic foods such as jicama & leeks
- Herbal tea, black tea, green tea
- Sulfur – containing veggies such as onions and garlic

2. Eat Less Frequently

- Starchy veggies such as white potatoes, corn, peas, squash
- Legumes such as peas & brans
- Nightshades such as eggplant, peppers, and tomatoes
- Non-tropical fruits (w/low glycemic index – berries)
- Pastured chicken
- Grass-fed beef
- Wine (limit to one glass a few times per week)
- Coffee

3. Avoid

- Sugar & other simple carbohydrates including bread (white & whole wheat), pasta, rice, cookies, cakes, candy, soda
- Fruits with high glycemic index (i.e. pineapple, etc.)
- Grains
- Gluten
- Dairy – occasional cheese, plain yogurt or organic whole milk, is ok
- Processed foods
- High mercury fish (tuna, shark, swordfish)

4. EXERCISE

The most relevant benefits of exercise for cognition include:

- Reduces insulin
- > Ketosis & > BDNR (neuron support)
- > size of hippocampus (key area of memory)
- Improves vascular function (key for neuronal & synoptic health)
- Reduces stress and inflammation
- Improves sleep (necessity for cognitive health)
- > survival of newborn neurons (neurogenesis creates new ones)

How best to do?

- Combine aerobic & weight training – 45 – 60 mins/day for 4-5 days per week

5. INFLAMMATION, AGING & AZD

Direct link between inflammation & AZD.

With constant state of inflammation (even if mild) leads to CVD, Cancer, Arthritis, Accelerated aging, and AZD.

Many things can cause inflammation:

- Infection (viruses, bacteria, fungi)
- Free radicals
- Advanced glycation end products (AGES)
- Trauma – bruises, sprains, broken bones
- Damaged proteins
- Lipids – oxidized LDL

HOW TO MEASURE INFLAMMATION

a. C-Reactive Protein (CRP)

Made by liver in response to inflammation

Measure high-sensitivity CRP (hs-CRP)

GOAL → hs-CRP < 0.9 mg/dl

Check for cause & fix

Causes:

- Too much sugar or simple cabs
- Trans fats
- Leaky gut
- Gluten sensitivity
- Poor oral hygiene
- Other toxins

b. Ratio of albumin to globulin (AIG)

s/b at least 1.8

c. Ratio of Omega-6 (pro inflam) to Omega-3 in RBC (anti inflam)

6/3 ratio s/b < 3.0 but not < 0.5 (inc. hemorrhage risk)

d. Interleukin – 6 (IL-6) and tumor necrosis factor alpha (TNFX)

Cytokines are dispatched in response to inflammation
2 cytokines that > inflammation in IL-6 + TNFX

e. GOALS

→ hs-CRP < 0.9 mg/dl

→ albumin ≥ 4.5 g/dl

→ A/G ratio ≥ 1.8

OPTIONAL TARGETS

→ Omega 6 / Omega 3 ratio = 0.5 - 3.0

→ IL-6 < 3 pg/ml

→ TNF alpha < 6.0 pg/ml

f. Inflammation Fixes

Very important driver of cognitive decline

Once lab tests have shown the sources of inflammation, reduce it:

1. Resolve it

- Supplement called specialized pro-resolvin, melatonin (SPMs)
  - SPM Active®
  - Resolvins*
  - Protectim*
  - Maresins*

*resolution agonists produced by the body at the site of inflammation.

SPM Active® (2-6 capsules/day for 30 days), but must remove underlying cause first. SPM help restore the missing resolution agonists.

2. Inhibit new inflammation.

   - Use anti-inflammatories:
     - o Omega-3 (1g/day of Omega 3 DHA from fish oil, krill, or algae)
     - o Curcumin (1g/day) with foods or on empty stomach

3. Other anti-inflammatories

   - Ginger
   - Cinnamon
   - Pregnenolone
   - Cloves
   - Thyme
   - Green leafy vegies
   - Beets
   - Broccoli

   Do not use NSAIDS (ibuprofen, etc.) as they can damage kidneys and gut.

   Remove all obvious sources (gum disease oral poor oral hygiene, infection, auto-antibody triggers, etc.)

   If inflammatory markers still test high, check for auto-antibodies and treat accordingly. (Rheumatoid Arthritis, Lyme disease, etc.)

6. VITAMIN D_3

Vitamin D activity is associated with cognitive decline. Inside cell it binds to the vitamin D receptor (VDR) allowing vitamin D to enter the nucleus (loc. Of DNA) & turns on over 900 genes. These genes do:

- Bone metabolism
- Suppress Tumor information
- Reduce inflammation
- Assist in creating & maintaining brain synapse

Sunlight → Cholesterol Molecule (7-dehydrocholesterol) → Inactive Vitamin D_3 → Active Form

TEST

Old: 25 – hydroxycholecalciferol (inactive)
20-30 ng/ml
Target s/b – 50-80 ng/ml

Optimal Dose:

Use 100x rule for optimal dose of VIT D (type D_3). Subtract current value from goal & multiply by 100 to get dose in IU's

Exp. IR value = 20

Goal = 50

Var 30 x 100 = 3,000 IU D_3

7. HORMONAL STATUS

a. THYROID

Suboptimal is common in AZD

Drives speed of metabolism

Meas. Metabolic speed by taking basal body temp.

- Use standard thermometer
- Place under arm pit for 10 min before getting out of bed in A.M.
- s/b 97.8 – 98.2 F
- If lower, you have low thyroid function

Also impacts reaction speeds (slows)

Also impacts heart rate & mental alertness

Also impacts how long you sleep, hot or cold feeling, weight gain, depression, and more.

SCI, MCI, Dementia patients are typically suboptimal

TEST FOR THESE GOALS:

→ Free T3 (active T3)	3.2 – 4.2 pg/ml
→ Free T4	1.3 – 1.8 pg/ml
→ Reverse T3 (inhibits)	< 20 ng/dl
→ TSH (thyroid stimulating hormone)	<2.0 microIU/ml
→ Ratio (Free T3 x 100)/reverse T3	≥ 20 ng/dl

b. ESTROGENS & PROESTERONE

Estrogens
Estradiol
Estriol
Estrone

Estrogen binds to its receptor & activates an enzyme (ADAM10) that cleans APP so that it sends out the synapse – supporting duo of sAAP alpha & CTF. Estrogen helps prevent dementia. Mayo study shows that women who have ovaries removed by age 40 w/o HRT (hormone replacement therapy) have 2x risk of AZD.

Ratio of estradiol / progesterone: high ratio associated w/poor memory

GOALS

→ Estradiol	50-250 pg/ml
→ Progesterone	1-20 ng/ml
→ Est/Prog Ratio	10-100

c. Testosterone (men & women have it)

Supports survival of neurons in men.

Men in lower quintile of testosterone concentration are at an increased risk for AZD.

GOAL

- Total testosterone 500-1000 ng/dl
- Free testosterone 6.5 – 15.0 ng/dl

d. Cortisol, Pregnenolone & Dehydroepiandrosterone (DHEA)

d.1 Stress is a major contributor to cognitive declined. Chronic stress is the worst kind.

Stress activates the "HPA axis" (hypothalamic – pituitary-adrenal axis)

STRESS → Hypothalamus → Corticotrophin – releasing factor (CRF)
↓
Stimulates pituitary gland to release ACTH (adrenocorticotropic hormone) to blood.
↓
Adrenal glands react to release cortisol & other stress related hormones.

High levels of cortisol damage neurons, especially in the hippocampus
High levels of cortisol Therefore: memory loss occurs

Chronic Stress → "dysfunction of HPA axis" (old term "adrenal fatigue"
Axis may then not produce enough stress hormones to deal with infection, toxins, or lack of sleep – all contributing to cognitive decline.

Rapid cortisol reduction alone can cause loss of neurons in the hippocampus.

d.2 Pregnenolone – Master steroid hormone from which all others are derived.

High stress periods divert Pregnenolone to produce stress hormones, leaving too little to produce optimal levels of sex hormones.

Pregnenolone supports memory & is neuroprotection Therefore: insufficient levels are a risk factor for cognitive decline.

d.3 DHEA – like pregnenolone, DHEA is a "neurosteroid" that supports the response to stress.

Measured on DHEA sulfate in blood or saliva.
(Also 24-hour urine specimen if above test indicates it is low or high)

GOALS

→ Cortisol (morning) 10-18 mcg/dl
→ Pregnenolone 50-100 ng/dl
→ DHEA sulfate 350-430 mcg/dl WOMEN
→ DHEA sulfate 400-500 mcg/dl MEN

e. Hormonal Balance

1. One of most effective and critical parts of ReCODE, but difficult to optimize. Must consult expert in bioidentical (BID) hormone replacement (HRT) who also has experience w/Cog. Dec. (especially women)

   Bioidenticals (some molecular structures as the ones made in your body). BID estrogens are:
   - 17 β-estradiol
   - estrone
   - estviol

   Non-BID estrogen is derived from urine of pregnant mules (source of drug Premarin).

2. Thyroid status: good measure is basal temp in the morning (under arm) of at least 97.8° (36.5° C). If < then thyroid is suboptimal (common w/Cog. Dec.)

   Thyroflex (reflex time measure) is another way to measure thyroid.

   Thyroid does not work alone, but in concert with other hormones, so cannot look at in isolation.

   Major active hormone is T3.

   Usual treatment is T4 (levothyroxine, Synthroid) – but may not easily convert to T3.

   Combo is preferred (T3+T4) such as Armour Thyroid. Or "NO Thyroid" or "Nature--Thyroid"

   Check iodine levels as it is needed for body to produce. If low take iodine pills (1x/day or kelp)

3. Estradiol & progesterone (women)

   They have brain protective effects, beneficial cognition effects, and a direct effect on molecular balance that drives AZD.

   Estrogen, alone, is not helpful in AZD. Estradiol may increase risk for uterine cancer & breast cancer.

   No dose consensus for Estrogens

   - 80 pg/ml is Osteoporosis threshold
   - 30-200 pg/ml treatment range

- Measurement via saliva, 24-hour urine, or other methods are not agreed upon.

Progesterone

- 100 mg – 200 mg of bioidentical such as Prometrium at bedtime.
- Target is 1-20 ng/ml – Monitor symptoms (mood & lethargy).

Estradiol or estradiol– estriol combo) is taken transdermally or transvaginally (oral can cause liver damage.)

Women with T3 SCI, MCI or AZD must optimize their hormone levels. Many T3 women can trace the onset of Cog. Dec. to menopause or perimenopause.

4. Testosterone

Optimal levels support synaptic maintenance.

MEN: If total testosterone < 300 ng/dl
-OR-
If free testosterone < 6 pg/ml

Need to optimize.

WOMEN: GOAL

For testosterone - 30-70 ng/dl

MEN – Monitor PSA for prostate cancer and calcium score or treadmill for CVD.

Do not stop suddenly as it can exacerbate Cog. Dec.
Taken off over several months.

5. Adrenal Function: cortisol, pregnenolone, and DHEA

Stress triggers cortisol which can damage hippocampus neurons.

Pregnenolone is the master steroid from which estrogens, testosterone, and cortisol (among others) are derived. When stressed, pregnenolone used to make cortisol, reduces ability to make estradiol or testosterone.

OTC Pregnenolone supplements 10-25 mg/day to get a level of 50-100 ng/dl.

If morning cortisol is low (< 8.0 mcg/dl) may be a sign you respond poorly to stress. If morning cortisol is high (>18 mcg/dl) – check for unknown stressors such as ongoing infection.

8. METALS

a. Copper (Cu) & Zinc (Zn)
> Cu & < Zn associated with Dementia

Most people have > Cu & < Zn

Cause: Cu piping? Vitamins?
Zn poor diets & poor absorption of Zn (need more acid in stomach)

AZD Type 3 (toxic) have very low levels of Zn in many cases. (50% lower than healthy people)

Low Zn > sensitivity to toxins such as mercury and mycotoxins from mold

Zn supplements enhance cognition.

Cu & Zn are "competitive". Too much Cu causes too little Zn.

Cu by its chemical nature is reactive and can encourage formation of free radicals which are damaging to cells.

Zn is not, and is part of over 300 different proteins. Zn does not form free radicals like Cu.

Zn is critical for insulin synthesis, storage & release

Zn deficiency reduces insulin signaling – a key feature of AZD.

Zn deficiency increases the level of autoantibodies (a source of inflammation)

Zn deficiency increases oxidative damage and aging

Zn deficiency reduces neurotransmitter signaling

All of the above are characteristic of or contributes to cognitive loss even w/o AZD.
Cu & Zn blood levels s/b approx. 100 mcg/dl (1:1 ratio)

Ratios of 1.4 or higher have been associated with dementia.

Most Cu is bound by proteins like ceruloplasmin. To determine free Cu (Cu not bound by protein), measure Cu minus (3xceruloplasmin): s/b < 30

GOALS

→ Cu: Zn ratio	0.8 – 1.2
→ Zn (serum)	90-110 mcg/dl
→ Zn (RBC) (better accuracy)	12-14 mg/l
→ Cu – (3x ceruloplasmin)	≥ 30

b. RBC (Red Blood Cell) Magnesium (Mg)

Mg critical for brain function.

AZD inflicts worst & earliest havoc on the hippocampi (1 left side, 1 right side of brain) & neighboring entorhinal cortex

Likely each hippocampi are low in mg w/AZD or cognitive decline.

Mg & threonine (amino acid) = improved cognitive function

GOAL – Measure in RBC, not serum
→ RBC Mg 5.2-6.5 mg/dl

c. SELENIUM (works with Glutathione)

Cleans up free radicals (molecules with unpaired electrons that damage cell membranes, DNA, protein, and overall cell structure)

In this process of cleanup, Glutathione is used up.

Low Glutathione contributes to inflammation, toxicity, and loss of support for synapses
→ all 3 types of AZD!

Selenium plays role in regenerating Glutathione

Therefore: less than optimal selenium associated with Cog. Dec.

GOAL

→ Selenium (serum) 110-150 ng/ml
→ Glutathione (GSH) 5.0-5.5 micro molar

9. HEAVY METALS

- Are neurotoxic

a. MERCURY (Hg)

- Mercury (Hg) mostly found high in large, older, fish (tuna, swordfish, orange roughy , and shark-especially thin fish)

  SMASH fish are safer (salmon, mackerel, anchovies, sardines, & herring)

  Hg in fish is organic mercury – typically methylmercury which occurs when microorganisms act on Hg

- Dental amalgams (inorganic Hg) are another primary source.

- Can be distinguished in blood & urine tests so you determine source

- Hg can induce Aβ plagues and neurofibrillous tangles
- Methyl mercury destroys the parts of glutathione that mop up free radicals

TEST: Blood not good. Urine is better. 6 hour collection, following chelating agents Hg Tri-Test (Quicksilver Scientific) uses hair, urine & blood without need for chelation.

b. ARSENIC (As)

- Groundwater is a more common source
- Chicken (organic chicken is best)

- Implicated in Executive Function Disorder, reduced mental activity, and deterioration of verbal skills and depression
- Symptoms all similar to Type 3 AZD (toxic)
- Also impacts the HPA axis

TEST: Avoid seafood for 3 days prior (seafood has non-toxic organic forms_ to prevent false positive.

c. LEAD (Pb)

- Epidemiological & toxicological evidence for Cog. Dec. has been known for a very long time.

d. CADMIUM (Cd)

- Dementogen & carcinogen
- Acts with Pb & As to enhance AZD type brain changes
- Cd found in cigarette smoke, chemical factories, paints (red & yellow)

e. ALUMINUM

- Do not know if it impacts AZD.
- Studies don't support it, but also don't disprove it.

NOTE: QuickSilver Scientific also has blood tests for other metals including:

Calcium, Chromium, Copper, Lithium, Magnesium, Molybdenum, Selenium, Zinc, Aluminum, Antimony, Arsenic, Barium, Cadmium, Cobalt, Lead, Mercury, Silver, Strontium, & Titanium.

GOALS

Hg, Pb, As, Cd < 50th percentile (QuickSilver)

-OR-

Standard lab blood levels:

Hg < 5 mcg/L

Pb < 2 mcg/dL

As < 7 mcg/L

Cd < 2.5 mcg/L

f. Metal Homeostasis

Amyloid precursor protein (APP) responds to metals such as iron, copper, and zinc.

1. Mercury

If mercury (Hg) is high (especially in organic Hg) it may be helpful to have amalgam fillings removed by a biological dentist.

Must remove Hg from system. QuickSilver uses a method gentler than heavy chelation. Uses pulsed treatments that activate gene called Nvf2 which helps the body eliminate toxic metals.

2. Copper (Cu) & Zinc (Zn)

Both s/b N 100 mcg/dL (1:1) – Cu/Zn

Max 1.3:1

Zn deficiency & Cu overload = Cog. Decline

High CRP (inflammation) attributes to bad ratios

Treat:

a. Zinc picolinate → 25 – 50 mg/day (50 max!)
b. Alpha-lipoic acid (antioxidant) → 30 – 60 mg/day.
   Prevent oxidative damage from copper
c. Vitamin C (chelates & removes copper) → 1 – 3g daily

3. Pyridoxine (Vitamin B6)

   Enhances detox

   100 mg/day

4. Manganese

   Supports antioxidant enzymatic effects

   15 – 30 mg/day

5. Stress reduction

6. Avoidance of vitamins with high copper content

10. SLEEP

- How sleep affects cognition (positively)

   a. Alters the cellular anatomy of your brain, allowing a cleansing.

      During sleep the extracellular space (between the cells) expands allowing more Ca & Mg ions to flow through.

      This is thought to flush out cellular debris including amyloid.

   b. Sleep associated with reduced formation of amyloid.

   c. Improves insulin sensitivity (while sleeping, not eating)

   d. During sleep – cells activate Autophagy (cells recycle components like damaged mitochondria, misfolded proteins, etc.). Without Autophagy – all "junk" collects and interferon with cell cleansing.
   Vs Apoptosis – programmed cell death. Biochemical events leading to cell changes (morphology) and death

   e. Sleep is a time of repair: growth hormones increase during sleep repairing cells. New supportive brain cells are produced & other reparation processes.

   f. Sleep Deprivation

      - Lack of sleep impairs cognition & increased risk of obesity, diabetes, & SCD. (All are AZD risk factors)
      - Can cause cravings for sugar, bad fats, other bad foods more conducive to AZD

g. Sleep Apnea (SA)

Where breathing temporarily stops. Big sign is heavy snoring.

Quality of sleep is inadequate for cellular restoration
75% of SA patients are undiagnosed.
Sleep study yields Apnea – Hypoxia Index (AHI) indicating the # of times per hour you have stopped breathing.

GOAL: AHI <5, Target is 0

If negative on SA test, but still sleepy during day, check about UARS (upper airway resistance syndrome) which can mimic SA. Test is done sleeping but with sensitive pulse – oximetry and esophageal pressure monitor.

c. Sleep Improves Brain Function

1. Sleep Apnea must be identified & treated (CPAP)

2. Try to get close to 8 hours per night w/o pills (Rx)

HELP: Melatonin is ok – 0.3 mg to 0.5 mg (up to 20mg). With excess you wake up early (after a few hours) generally sleep one night per week.

Middle of the night awakening contributes to cognitive decline. Potential causes:

- Menopause
- Hormonal imbalance (especially low progesterone)
- Depression
- Stress

HELP: If you are ruminating (unable to stop going over problems in your head) you may take:

- Tryptophan (Trp) 500 mg at bedtime -OR-
- 5-Hydroxytryptophan (-100 to 200 mg) enters brain more readily than Trp.

Avoid both if taking SSRI (selective serotonin reuptake inhibitors) – antidepressants like Prozac or Zoloft. Taken with above can lead to serotonin syndrome (fever, agitation, sweating and diarrhea.) Synapses get flooded with too much serotonin.

d. Another cause of awakening mid-night is reduced progesterone (affect both women & men) if levels relative to estradiol (ratio E: P too high) P has relaxing effect.

HELP: Bioidentical oral progesterone – 100 mg before bed

e. w/men, low progesterone may = cow testosterone (progesterone is a precursor for testosterone). Low testosterone is a risk factor for cognitive decline. Must optimize testosterone levels.

f. GERD (gastroesophageal reflux) is not likely w/Ketoflex 12/3, but when it occurs avoid PPIs (e.g. Prevacid). Stomach acid needed for proper food mineral & vitamin absorption.

In some cases of GERD, the acid actually reduces reflux since it causes the lower esophageal sphincter to close.

g. Good Sleep Hygiene

- Keep room as dark as possible (more melatonin produced). Use mask if needed
- Keep environment quiet. Turn off electronics & avoid EMFs (electromagnetic fields)
- Slow down before trying to sleep
- Go to bed before midnight so early morning noise won't wake you
- No exercise for 2 hours before bedtime to reduce adrenaline levels
- Exercise early in the day to insure adrenaline levels are low at night
- Avoid blue light (LEDS) at night
- Keep TV out of bedroom
- Avoid heavy evening meals
- Keep hydrated but don't drink a lot too close to bed time

h. STRESS

Running a system at a level beyond what it was meant to operate is the definition of stress. Our bodies can handle intermittent stress, but not constant, long term stress. Stressors include all the typical issues of daily life:

- Sugar laden diets
- Late nights
- Work anxiety
- Poor sleep
- Poor nutrition
- Toxic chemical exposure
- Financial pressure
- Health concerns
- Familial issues

Stress increases cortisol, which is a brain toxin, at high levels (especially the hippocampus – which is one of the first structures assaulted by AZD.)

Stress also increases risk factors for cognition decline:

- Blood glucose
- Body fat
- Obesity risk
- Carb craving
- Leaky gut
- Inflammation

- Blood-brain barrier leaks
- Calcium release
- Hyperstimulation of neurons
- CVD risk

Stress reduces protective factors against AZD -synapse preserving ones.

Stress factors in all types but is especially strong in Type 3 (toxic) AZD, MCI or SCI.

Onset of cognitive decline often coincides with period of great stress.

Reduce stress by removing stressors, or, when not possible:

- Meditation
- Yoga
- Diaphragmatic breathing (belly, not chest)
- Exercise time reduction (if over-doing it)
- Caffeine reduction
- Alcohol
- Massages
- Music
- Laughter

11. Cholesterol (Chol) & Other Lipids

Low (not high) is associated with Cog Dec

- Vascular disease contributes to cognitive decline
  - Raises AZD risk
  - May cause vascular dementia

When TOT CHOL < 150, more likely to suffer brain atrophy (shrinking).

CHOL is key part of cell membrane.

- Real culprit is damaged Chol & related lipid particles

GOALS:

• LDL-p (LDL particle number)	700-1,000
-or-	
• sdLDL (small dense LDL)	<20 mg/dl or 20% of LDL
-or-	
• Oxidized LDL	<60 U/L
• TOT COL	>150

12. Leaky Gut/Gastrointestinal (GI) Permeability

a. Common cause of inflammation
b. In gut, cells lining GI tract maintain tight junctions (cell "caulk" is a protein complex w/occluding)
c. This Tightness keeps food on the inside of gut, delivering nutrients to cells throughout the body.
d. Can cause leaks:

- Gluten sensitivity
- Pesticides
- Soft drinks
- Alcohol
- Sugar
- Processed foods
- Preservatives
- Inflammation
- Chronic Stress
- Yeast
- Aspirin
- Acetaminophen

e. If large protein fragments leak out of gut, they can cause inflammation (body reads these as foreign & immune systems is triggered).

   Inflammation is a type 1 AZD cause

f. Crucial to keep large protein fragments from leaking out of gut & entering blood stream.

g. Gut porosity can also allow bacteria, yeasts, & fragments to enter bloodstream

   Persistent low-level inflammation may trigger autoimmune disease such as:

   - Multiple Sclerosis
   - Rheumatoid Arthritis
   - Lupus Erythematosus

   Plus it can contribute to AZD.

h. Tests for Leaky Gut

   Q1) Ingest 2 different sugars

   - Lactulose – does not normally pass gut barrier
   - Mannitol – passes through gut barrier "normally"

   One or more end up in the urine via the bloodstream.

   Mannitol in urine tells you the gut is not failing to absorb but if lactulose is present, it indicates leaky gut.

   Q2) Evaluate immunological response when gut is breached. Body produces antibodies against bacteria that leak due to lipopolysaccharide (LPS) on surface of the bacteria.

   Q3) Antibodies to the barrier proteins (zonulin/occludin) indicates leaky gut.

TEST B/C:

- Cyrex Array 2

ALT: Eliminate suspect foods & reintroduce one at a time & observe for symptoms

i. Healing the Gut

1. Very common problem, very important to treat.

   If Cyrex Array 2 is positive or if you know you have food sensitivity and/or bloating, constipation, or loose stools, then the integrity of your gut lining is compromised.

   Healing your gut reduces inflammation, improves nutrient absorption, enhances immune responses, supports the microbiome (increases products of microbiome such as hormones and neurotransmitters)

2. Potential triggers:

   - Sugar
   - Gluten & other grain allergens
   - Dairy
   - Chemicals in processed foods (preservatives, dyes, binders, sweeteners, etc.)
   - Herbicides (like glyphosate)
   - Pesticides
   - GMO foods
   - Alcohol
   - Antibiotics including concentrated animal feeding operations (CAFOs)
   - Anti-inflammatories / NSAIDS (aspirin, ibuprofen)
   - Steroids
   - Stress

3. <u>Complimentary Measures:</u>
   - Bone broth (collagen, amino acids, minerals, vitamins)
     - Used by Okinawan people who eat minimal meat.
     - Helps seal the gut and strengthens the intestinal barrier
   - Colostrum capsule
   - L-glutamine capsule
   - Zinc corrosive
   - SCD diet, using specific carbohydrates
     - https://draxe.com/scd-diet/

4. Bone broth details:
    - May use as base for soups, stews, etc.
    - Some advocate drinking for days to weeks while eliminating then reintroducing foods once at a time.
    - Use as adjunct to the Ketoflex 12/3 diet
    - Buy it or make your own
    - Can be purchased on-line

    Should be healing in 3-4 weeks.

5. Retest by Cyrex Array or other method.

    Once healed, can now include probiotics & prebiotics into diet. Sources best from food:
    - Probiotics (bacteria) – fermented foods (sauerkraut, kimchi, etc.); if capsule use 30-50 billion cfo
    - Prebiotics – fiber rich foods (jicama, onions, leeks, and garlic)

6. Core Species of Bacteria Recommended for Probiotic
    - *Lactobacillus plantarum* (kimchi, sauerkraut, fermented vegetables)
    - *Lactobacillus acidophilus* (fermented dairy)
    - *Lactobacillus brevis* (sauerkraut, pickles)
    - *Bifidobacterium lactis* (fermented dairy)
    - *Bifidobacterium longum* (fermented vegetable & dairy)

    Once optimized your gut microbiome you should experience no bloating, constipation, or diarrhea. Having eliminated an important source of inflammation, you will also eliminate toxins more efficiently and improve cognition.

13. Blood-Brain Barrier Permeability

AZD brains have shown microbes
- Bacteria
- Viruses
- Fungi
- Other microbes

Low levels of pathogens, not active like meningitis & encephalitis, can cause inflammation.

Bacteria *Porphyromonas gingivalis* has turned up repeatedly in AZD brains as have some proteins made by this microbe. This is an oral bacteria.

Other oral bacteria have also been found:

- *Fusobacterium nucleatum*
- *Prevotella intermedia*

Also:

- *Herpes simplex* virus (HSV)
- HSV lives in nerve cells that supply your face & lips (trigeminal ganglion cells).
- Can migrate via nerves to brain & cause inflammatory response.

Historically, *Treponema pallidum* (syphilis) – bacterial spirochete (corkscrew shape) can live in body for decades eventually in feeding the brain and causing dementia.

Also: Lyme disease spirochete, *Borrelia burgdorferi*, also found in AZD brains. Carried by deer tick. Ixodes. 50% of Ixodes bites infected with additional microbes including *Ehrlichia* (infects WBC); *Babesia* (relative of malaria parasite which infects RBC); and *Bartonella* (infects blood vessels.)

Also: Fungi found in AZD brains.

AZD reflects a protection response to many infections, inflammatory, or toxic insults. "Leaky" blood-brain barrier can allow access to brain. Microbes can also access the brain via the nose, gut/vagus nerve that connects the gut to the brain stem, and the eye. AZD T3 – nasal & sinus access to the brain is abs critical.

TEST Cyrex Array 20 – Negative (goal)

14. Gluten Sensitivity & Related

- Gut-Brain connection critical for cognition
- Celiac disease is associated with severe gluten intolerance (5% of population)
- Majority still suffer from gluten damage to GI tract
- Gluten sensitivity test

TEST 1: Assess tissue transglutaminase antibodies in serum (standard blood test)

TEST 2: Cyrex Array 3

Cyrex Array 4 – Sensitivity to rye, barley, sesame, oats, or rice.

GOAL: Test 1 – Negative

Or

Cyrex Array 3 – Negative

Cyrex Array 4 – Negative

15. AUTOANTIBODIES

When the immune system is causing war on your brain, it is important to know, since autoantibodies can attack brain proteins and add to Cog Dec

TEST/GOAL: Cyrex Array 5 – Negative

ANNECDOTAL

- Female, since y/o hysterectomy has had depression
- Had HRT (levels not known)
- 4 years later had word difficulty, trouble driving & following recipes & other instructions.
- After several days of rest, mood & cognition increased. Both declined markedly w/sleep deprivation, viral illness, or other stressors.
- MOCA was 19 (26-30 normal)
- Exam points to deficits in frontal, temporal, and parietal lobes.
- MRI – Normal (but no volume done)
- PET – Abnormal, w/residual glucose utilization in the parietotemporal and frontal region, characteristic of AZE.
- Testing revealed levels of autoantibodies against thyroid protein (thyroglobulin/ >2000 x normal)
- High C4a & TGF – β1 (typical of AZD T3)
- APOE 3/3
- Treated for CIRS (which can be induced by mycotoxin or Lyme disease or other pathogen). With Cholestyramine (binds toxins in the gut and intranasal.
- VIP (vasoactive intestinal peptide) Supports neurons and RECODE.
- Significantly improved over several months.

16. TOXINS, T3 AZD, and CIRS (Chronic Inflammatory Response Syndrome)

a. Dementogens

- Statins caused APP cleavage into the destructive Quartet that includes cell death.
- Other dermentogens found in T3 AZD, is mycotoxins made by molds such as Stachybotrys, aspergillus, penicillium, and Chaetomium.
- Est. mold contributes to 500,000 cases in the USA.
- CIRS (Chronic Inflammatory Response Syndrome) Symptoms:
    - Asthma
    - Chronic fatigue
    - Fibromyalgia
    - Nose bleeds
    - Rashes
    - Shortening of breath
    - Cognitive decline
    - Headaches
- All appear to be related to the so-called "innate immune system." (IIS)
- In CIRS the IIS activated by mycotoxins or other invaders for long periods of time.
- 25% have an IIS chronically activated.

b. TEST & GOALS

- Genetic blood test for HLA – DR/DQ – For 25% of population this gene is activated for CIRS propensity
- Blood:
    - C4a < 2830 ng/ml
    - TGF – β1 < 2380 pg/ml
    - MSH = 35-81 pg/ml
- Urine:
    - Test for most dangerous mycotoxins: trichothecenes, ochratoxin, aflatoxin, gliotoxin
- Urine Goal:
    - Test negative for all mycotoxins

c. Rhinosinal Microbiome (nose & sinuses)

- "Quickest way to brain is thru the nose, throat, and sinuses"
- Affected by chronic rhinosinusitis (nose & sinus inflammation)
    - Mold
    - MARCONS (Multiple antibiotic resistant staph bacteria that form protective coatings called biofilm and are resistant to antibiotics).
- Products (toxins) secreted by above can enter the brain via their proximity to brain.
- If lab results indicate an increase in C4a (immune symptom component that goes up with biotoxins) and if you have symptoms suggestive of T3 AZD, or you have chronic sinus problems, you must address this microbiome.
- See Dr. R. Shoemaker's website: http://ww.survivingmold.com

d. Treatment

- If Marcons present, they s/b treated
    - BEG (nasal spray): Bactroban (mupirocin), EDTA, (gentamicin)
    - Mold – itraconazole antifungal or immune enhancer guduchi (*Tinospere cordifolide*)
- Restore optimal microbiome
    - Probiotics for nose & sinuses
    - ProbioMax ENT
    - Restore (nasal)
    - Kimchi juice swab
- Remove source of pathogen
    - Molds at home or work https://www.mycometrics.com

e. Additional Toxin (T3 AZD) Information:

- May be the most difficult part of ReCODE.
- Use Shoemaker Protocol for mycotoxin exposure. http://ww.survivingmold.com
- History required to diagnose this:
    - General anesthesia (how many times?)
    - High Hg Fish (tuna, shark, swordfish, etc.)? How often?
    - Mold in house, car, or workplace?
    - Do you eat preserved or nonorganic foods?
    - Tick bites?
    - Medications taken
    - PPI's taken?

- How much alcohol?
- Use makeup, hairspray, or antiperspirant?
- How often do you sweat (eliminate toxins)?
- Constipation? (B.M. eliminates toxins)
- Drink at least 32oz of purified water daily? (urination eliminates toxins)

TREATMENT

1. Pathogens
    - Shoemaker Protocol http://ww.survivingmold.com
    - Experimental functional medicine specialist in biotoxins
    - Treatment based on test results may indicate MARCONS, mold species, sinus microbiome treatment, etc.

    Ways to inactivate & execute pathogen associated biotoxins and increase cognition to T3 AZD, MC2, and SCI:

    - IV glutathione 2x/week (antioxidant & antitoxin) -OR- Liposomal glutathione, nebulized glutathione, or N-acetylcysteine capsule.
    - Intranasal VIP (vasoactive intestinal peptide) provides trophic support to brain. Used after MARCONS is negative.
    - Detoxifying foods:
        - Cilantro
        - Cruciferous, Vegan
            - Broccoli
            - Turnips
            - Water cress
            - Kohlrabi
            - Rutabaga
            - Arugula
            - Horse radish
            - Maca
            - Rapini
            - Claikon
            - Wasabi
            - Bok choy

- Avocados
- Artichokes
- Beets
- Dandelion greens
- Garlic
- Ginger
- Grapefruit
- Lemons
- Olive oil
- Seaweed

- Bind toxins in your gut with cholestyramine, welchol, or guggul (or, especially for metals, chlorella) and by enhancing excretion via sauna followed by showering with non-emollient soap (e.g. Castile); and by urination following hydration with filtered water.
- Bioidentical hormone optimization

2. Restore microbiome by following steps listed for probiotics for nose & sinuses.

3. Remove source of pathogen
   a. Molds
   b. HEPA filters (IQAir)

17. <u>MITOCHONDRIAL (MITO) FUNCTION</u>

MITO supplies energy that allows cells to function.

Convert energy from food & oxygen we breathe into the molecule ATP, which powers the cell.

MITO can be damaged by:

- Antibiotics (since MITO are postulated to discard from bacteria, antibiotics will damage them)
- Statins
- Alcohol
- L-DOPA (used to treat Parkinson's)
- Griseofulvin (Rx for fungal infections)
- Acetaminophen (Tylenol)

- NSAIDS (aspirin, ibuprofen, etc.)
- Cocaine
- Methamphetamine
- AZT (for viral infection including HIV/AIDS)
- APOE 4 (maybe)

No direct test for MITO function, most look for childhood diseases, not dementia.

Current Test which may be used:

- Breath test
- Nuclear magnetic resonance tests
- MITO DNA sequencing
- Muscle biopsies

GOAL: No exposure to damaging agents

18. BMI (Body Mass Index) & Waistline

a) An unhealthy BMI raises risk for cognitive decline use on-line calculators to determine.

GOAL → For Optimal Cognition BMI 18-25

>26 – inc risk of T2 Diabetes, which > risk of AZD

<18 – Not sure, but could imply suboptimal nutrition and/or suboptimal hormonal stature.

b) Visceral fat is more accurate measure of metabolic stature. Determine by (especially look for liver fat)

- Ultrasound
- MRI
- Body composition analyzer - (Tanita Score of 1-12)
- Waistline *(Editor's note: some say 50% of height in inches)*

  Females < 35

  Males < 40

19. Genetics

Optimal diet differs if APOE "positive".

- Entire Genome sequenced for $1k to $1,600.
- Exome (Genome Part that codes for protein) $600
- Simply test for # copies of APOE (0,1,2)

Also:

- 23andMe (and others similar)

  Assess a large # or SNPs (single nucleotide polymorphisms – gene variants)
- Download 23andMe file, upload to other services like

  a. Promethease

  https://promethease.com/

  b. MTHFR Support

  http://mthfr.net/

  c. Editor's note: Found My Fitness (Dr. Rhonda Patrick)

  https://www.foundmyfitness.com/genetics

GOAL: Know APOE Status

ALT. GOALS: All SNPs related to neuro degeneration

- APP
- PS1
- PS2
- CD33
- TREM2
- CR1
- NLRP1

20. QUANTITATIVE NEUROPSYCHOLOGICAL TESTING (Links are in the Supplement)

Test status of memory & other aspects of cognition (organizing, calculating, and speaking)

a. Methods

1. MOCA (Montreal Cognitive Assessment) Test (Free)
   Available online and takes 10 minutes

Normal	26-30	
MCI	19-25	
MCI -> Dementia	19-22	w/difficulties of daily living
Dementia	<19	

Less sensitive and more useful for severely affected:

2. Mini-Mental State Exam (MMSE)
3. SAGE (Self-Administered Gerocognitive Exam)

More sensitive to early changes and providing more detail about brain region impacted. And give percentiles for age group and area of brain.

4. CNS Vital Signs
5. BRAIN HQ
6. Dakim
7. Lumosity
8. Cogstate

b. GOAL

MOCA 26-30

Get percentile via other tests

c. BRAIN TRAINING

Some say controversial, but the best data show otherwise.

On-line brain training includes:

- Posit Science (Brain HQ) 10-20 mins/day, 5x/week
- Lumosity
- Dakim
- Cogstate

One game called "Double Decision" reduced risk of dementia by nearly 50% ten years after training. This is better than any drug therapy.

21. IMAGING, CEREBROSPINAL FLUID (CSF), AND ELECTROPHYSIOLOGY
(EEG is one type)

a. MRI w/volumetrics to assess percentile score

- Neuroreader calculates for 39 brain regions
- NeuroQuant

b. PET (Position – emission tomography)

- Helps with difficult diagnosis
  (I.e. distinguishing between frontotemporal dementia and AZD)

c. AMYLOID PET

- Shows amyloid accumulations in the brain
- Problem – AZD cog. dec. Can occur w/o amyloid
- If PET is +, but no cog. dec. then it will be coming images not well correlated w/brain areas showing cog. dec.

d. TAU PET SCAN

- Shows better correlation w/specific brain area

e. CSF (from a spinal tap)

- Helpful if diagnosis is in question as in AZD there is a reduction in amyloid beta 42 and an increase in total tau & phospho – tau in CSF

f. EEG (Electroencephalography)

- Shows evidence of seizure (occurs in 5% of cases) including non-convulsive seizure
- Treat w/anticonvulsants

GOAL -> MRI Volumetrics Normal

- FDG – PET
- Amyloid PET
- tau PET
- EEG normal, w/no seizures

22. NEW TESTS FOR COGNITIVE DECLINE
(Soon to appear/novel)

a. Neural exosomes – tiny fragments of material expelled from the cells (sifting thru garbage)

Brain puts out neural exosomes, detritus and secretions into blood stream (billions of these in each oz. of blood)

So far have isolated exposomes:

- AZD "signature"
- > in Aβ
- > phosphorylated tau
- Insulin resistances "Signature"
  Can occur up to a decade before AZD

Future:

- Aβ42 (mainly associated w/AZD)
- Phosphor – tau
- Cathepsin D (protease assoc. w/AZD)
- REST (indicates levels of trophic support
- Phosphorylation ratio of IRS – 1 (I.R. or sensitivity)

b. RETINAL IMAGING

Back of eye is an extension of the brain looking for amyloid plaques – map size & location and then look for > or < after treatment.

Much clearer than PET scan

Amyloid in blood vessels can be seen (may cause hemorrhage) and these people must avoid blood thinners (fish oil, aspirin, etc.)

Neurovision Imaging is running clinical trials
(Dr Keith Black of Cedars-Sinai Medical Center)

c. NEUROTRACK and the MESIAL TEMPORAL LOBE
(Novel object recognition)

Neurotrack released the Imprint Cognitive Assessment Test
5-minute web based cognitive assessment that by tracking eye movements detects which objects are seen on novel. Detects impairment of the hippocampal & nearby structures.

23. OTHER CONSIDERATIONS

HISTORICAL/LIFESTYLE FEATURES

Life history gives clues, need to know:

- Suffered head trauma (auto accident, contact sports, etc.)
- General anesthesia
- Dental amalgams
- Eat high Hq risk
- Take medications w/brain effects
    - Valium
    - Antidepressants
    - Blood Pressure Pills
    - Statins
    - PPI's
    - Antihistamines
- Street Drugs
- Alcohol
- Cigarettes
- Good oral hygiene
- Surgical implants
- Liver, kidney, lung, or heart disease
- Snore
- OSA
- Hot-pressed oils (like palm oil) – Lose some of Vitamin E
- Eat foods high in trans fats or simple carbs
  (Vascular damage & I.R.)
- Chronic sinus problems (may be related to mold exposure)
- Have GI issues (Bloating or diarrhea)
  May indicate leaky gut
- Have mold in house, car, workplace
- Eat processed foods or non-organic foods (I.R./Toxin exp.)
- Tick bites
- Use PPIs (reduce acid needed for digestion: reduce uptake of 2n, vit B_{12} and other nutrients)
- Use makeup, hairspray, or antiperspirant
  (Toxic exposure)
- Don't sweat much (sweat eliminates toxin)
- Constipation (BM eliminates toxin)
- Don't drink enough purified water (urine removes toxin)

Summary: The Cognoscopy

Anyone over 45 y/o should take the tests.

ReCODE Protocol Summary

1. IR
2. Inflammation/Injections
3. Hormone, Nutrient, and Trophic Factor Optimization
4. Toxins (Chemical, Biological, & Physical)
5. Restoration & Protection of Lost or Dysfunctional Synapses

Best Practices

1. Sooner you start, the better your chances are for reversing and protection
2. Live your protocol for at least 6 months
3. Identify what is wrong; don't treat blindly
4. Keep optimizing (adjust as indicated)
5. Be diligent about lab values
6. Do what you can – you don't necessarily have to follow every part of the protocol
7. With each tweak of your protocol, try to notice over the ensuing days and weeks whether cognition gets better, worse, or neither
8. Don't let the perfect be the enemy of the good.
9. Document your cognition stature so you know where you stand, when you are improving, & when things need to be adjusted
10. Take advantage of social networks
11. Be careful about going off therapeutics' cold turkey
12. Stick with the program
13. You can start the program in phases.

The Best Responders Generally Include:

1. People who are at risk because of APOE stature but who do not yet have symptoms (no one has yet converted to AZD)
2. People with subjective cognitive impairment (SCI) have all improved.
3. People with early mild cognitive impairment (MCI) – w/MOCA score of 24+, best chance to improve. An MCI (amnestic MCI) responds best.
4. People with early AZD
5. Forms of cognitive decline – SCI, MCI, early AZD that are NOT T3 (toxic). Once "toxic" has progressed to AZD, treatment is more complex. MG toxicity is actually the most treatable T3.
6. People with cognitive changes who are otherwise healthy
7. People who have no brain atrophy on MRI or in whom the atrophy is restricted to the hippocampus.
8. People younger than 75
9. People who have supportive spouses & supportive physician

N. SUPPLEMENTARY MATERIALS (Including key web site links)

SEE THE SEPARATE DOCUMENT FOR SUMMARY TEST TABLES AND INTERVENTIONS INCLUDING GENETIC ASSESSMENTS:

Compilation and summary of the Key Tests & Interventions for ReCODE Protocol.

www.ClinicLibrary.com