REVIEW ARTICLE

Alzheimer's Disease: Prevention, Delay, Minimization, and Reversal

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ABSTRACT

Contrary to prevailing medical dogma, Alzheimer's disease (AD) and the associated cognitive decline of dementia is not incurable but can be prevented, minimized, and even reversed. At issue is whether the formation in the brain of amyloid beta (a piece of protein) and its accumulation in sticky, synapse-destroying plaques is the cause of the disease or merely a component of it or the normal brain's immune response to neuro insults. Another issue is whether AD is a single disease type or several distinct subtypes (three of them have been identified), or a combination thereof, that would require separate treatments. The above assertions have recently been posited and demand serious consideration. In a companion article, I reviewed the several hypotheses (theories) that have been advanced so far, including also the so-called tau hypothesis to explain the neurofibrillary tangles within neuron cells. Here, I review the above assertions beginning with our current knowledge of AD, explain why the presently approved drugs have at best been of limited palliative effect, and address the various neuro threats. I also analyze the known biochemical markers, the corresponding various tests (genetic and biochemical), and the related historical and lifestyle factors that are needed to assess the status of any given AD case. Treatment concepts are also set forth before prescribing individualized treatments.

Key words: Alzheimer's disease; amyloid beta; neurofibrillary tangles; tau hypothesis; biological markers; personalized treatment

INTRODUCTION

In an earlier article,[1] I reviewed the several (hypotheses) theories advanced so far for explaining Alzheimer's disease (AD) and proposed to do the same for the newest, most provocative one - that very recently proposed by Dr. Dale Bredesen, Professor of Neurology, and his colleagues at the University of California at Los Angeles.[2-4] Dr. Bredesen posited that all previous hypotheses (except the genetic hypothesis) had failed because premised on the wrong assumptions that AD is a single disease caused by the accumulation of amyloid beta plaques. In particular, he wrote, "*the idea of identifying the cause of the amyloid beta production, removing it, and then removing the amyloid, has not been tested*." This is strictly correct for any of the hypotheses advanced so far, and not just for the amyloid hypothesis alone. Nonetheless, it remains that the amyloid hypothesis is still generally accepted (perhaps erroneously), at least as one cause of AD. The issue is whether it is the cause of the disease, or merely an element of it, or even the normal immune response of the brain to neuro insults. Actually, additional hypotheses have also been advanced, including particularly the so-called tau hypothesis to explain the neurofibrillary tangles within neuron cells (interestingly, in a paper published in *Science Translational Medicine,* Harvard University researchers Robert Moir, Rudolph Tanzi and their coauthors have shown that amyloid beta can act as a natural antibiotic in the immune system).

Dr. Bredesen further claimed that there are three main subtypes of AD that are each driven by different chemical processes, each requiring a different treatment and that AD may exist in

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either one or a partial combination of these subtypes. He further described his book[2] as a "*manual for preventing and reversing the cognitive decline of early AD or its precursors, mild cognitive impairment and subjective cognitive impairment, and for sustaining the improvement*." Still further, he claimed that his manual also encompasses those people who have genetically inherited the ApolipoproteinE (ApoE) ε4 allele (the highest risk factor for AD). For convenience, I shall refer to Dr. Bredesen's hypothesis as the "INT hypothesis," where I stands for inflammation/infection, N stands for neurotrophy or suboptimal levels of brain nutrients, and T stands for toxic exposures. While it is a crisper exposition of the disease, the INT hypothesis is subsumed in the published literature, except perhaps and importantly for the neurotrophic aspect.

After a brief narration of the INT hypothesis, I will review the present AD situation, the origin of the disease and its underlying process, the limited palliative effects of current pharmacology, and how to address the various neuro threats to be able to prevent, minimize or reverse AD. I will subsequently detail the several genetic and biochemical tests needed to diagnose the AD status of any AD patient, including the complementary historical and lifestyle factors, and explain how to address them with a view toward a personalized treatment.

ON THE INT HYPOTHESIS

AD is the natural immune response of the brain to a variety of insults (or risk factors), approximately 36–40 by Dr. Bredesen's count, perhaps a little bit more. (Often in AD patients, 10–25 blood chemistry values described below are found to be sub-optimal, compared to 3–5 for people without AD symptoms). Under such an assault, often lasting for decades, the immune response has run amok. An otherwise normal, healthy, and protective brain "housekeeping" process has gone haywire. The defense mechanism includes producing the Alzheimer's associated amyloid. Being overactive in general, the chemically active immune system sometimes attacks the body's own tissues (an autoimmune disease). In sum, the physiological system is not functioning as intended.

AD is, therefore, the brain's protective response from three metabolic and toxic threats (which themselves have dozens of contributors) from which the acronym for the hypothesis derives:

1. Inflammatory insults (such as infections, trans fats, or other causes). Amyloid beta taken from humans protected laboratory animals against otherwise lethal infections, suggesting that AD develops when the brain perceives itself to be under attack from an infection. Production of amyloid then goes into overdrive to ward-off the attack;
2. Sub-optimal nutrient levels (both brain nutrients aka neurotrophic factors and body nutrients, hormones, and other brain-supporting molecules); and
3. Neurotoxic exposures and compounds (including biotoxins, which are poisons produced by microbes such as molds).

Threats 1 and 2 are intimately linked to metabolism, itself a function of our diet, level of physical activity, exposure to and handling of stress, and sleep insufficiency or deprivation. Since diet, physical activity, stress, and sleep also affect cardiovascular health and other aspects of our well-being, brain health is closely related to general health. The many conditions that increase the risk for AD - from pre-diabetes to obesity to Vitamin D deficiency and a sedentary lifestyle - are the result of what and how much one eats, exercises, manages stress, and sleeps.

ABOUT ALZHEIMER'S DISEASE

According to the Alzheimer's Association: "*A genuinely new Alzheimer's drug has not been approved since 2003, and the currently approved Alzheimer's medications are ineffective in stopping or slowing the course of the disease.... the four available Alzheimer's drugs may help lessen symptoms such as memory loss and confusion.... no drug can cure Alzheimer's or stop it from progressing."* Indeed, of the 244 experimental Alzheimer's drugs tested from 2000 to 2010, exactly one - memantine (Namenda) - was approved in 2003…and its effects are modest at best. Further, of the 10 most common causes of death, Alzheimer is the only one for which there was no effective treatment until, hopefully, the advent of the INT hypothesis and its underlying treatment program.

Current situation

Five reasons explain the current dreadful condition:

1. There is no drug that would prevent the disease to develop from earlier conditions - subjective cognitive impairment (SCI), mild cognitive impairment (MCI) - to full-blown AD. In brief, as of 2017, there is nothing that reliably prevents or slows AD. Drug targets are now focusing on brain inflammation (to be distinguished from infection), cholesterol buildup, and tau protein accumulation in patients' brains which correlate with (but not necessarily cause) cognitive decline. Furthermore, because diabetes increases risk for the AD, some scientists have even equated AD with "brain diabetes" and proposed using insulin nasal sprays as a potential treatment.
2. AD is worse than a fatal disease;
3. Dr. Alois Alzheimer (1864–1915), a neuropathologist, had described the amyloid plaques in the autopsied brain of "Auguste," the first patient he had diagnosed with presenile dementia. Laboratory studies on transgenic mice have also shown that AD is caused by the accumulation in the brain of amyloid plaques (pieces of a protein called, amyloid-beta (a peptide) [Aβ]) that stick to, and destroy, synapses by a series of demonstrated steps. Either intervening in or interfering with, those

steps or eliminating the Aβ plaques could, theoretically, arrest AD. Unfortunately, in humans, this did not prove to be the case for the extrapolation from laboratory mice to humans does not hold, at least in the case of AD. While the compounds tested performed as intended, the end result was not as expected. Thus, when antibodies that bind to the amyloid to remove it were tested, the amyloid was removed, but the patients either got no better or got worse; if the compound was designed to block the enzyme needed to produce the amyloid, again it performed well, but the disease still remained or worsened. These results invalidate the amyloid hypothesis (the so-called amyloid cascade hypothesis), all the theories based thereon, and all the mouse laboratory tests. In addition, the idea of identifying the cause of the Aβ production, removing it, and then removing the Aβ, has not been tested;

4. The other abnormality, the neurofibrillary tangles inside the neurons themselves (these are long stringy tangles of a protein called *tau*) have long been overshadowed by the focus on the amyloid plaques; and
5. AD may not be, as generally assumed, a single disease treatable with a single (or a combination of a few) drug(s).

Currently approved drugs limitedly alleviate symptoms

Since the formulation of the amyloid hypothesis as the cause of AD, hundreds of amyloid-removing compounds have been discovered. However, none of these proved to be effective. Two FDA-approved drugs are now generally employed, but neither treats the cause of AD and even less cures it:

1. Donepezil (Aricept): Acetylcholine (a neurotransmitter that carries signals along the synapses between the neurons) is reduced in AD. It is progressively destroyed by cholinesterase (an enzyme). Inhibiting ("blocking") this enzyme would theoretically slow down or even eliminate the destruction process, allowing more acetylcholine to remain. This is the rationale behind Donepezil (a cholinesterase inhibitor), and it has had modest success. Unfortunately, there are the following caveats: (a) Only the symptom of the problem is treated, not its cause; (b) responding to the inhibition of cholinesterase, the brain naturally produces even more cholinesterase, limiting the drug's efficacy; and (c) like all drugs, there are side effects (including diarrhea, nausea, vomiting, backache, joint pain, drowsiness, loss of appetite, and bradycardia).
2. Memantine (Namenda): It inhibits the transmission between neurons that takes place with the other neurotransmitter - glutamate. Memantine reduces the so-called excitotoxic effect (that is, the toxic effect associated with neuronal excitation). Unfortunately, it also inhibits the very neurotransmission that is critical to memory formation and may contradictorily impair cognitive function. It also presents the similar limitations as donepezil.

Other approved drugs are rivastigmine (Exelon) and galantamine (Razadyne). Currently, 36 novel symptomatic and disease-modifying anti-AD treatments are being tested in phase 2 or phase 3 clinical trials. In view of the limited symptomatic relief by drugs, other research has focused on natural supplements to treat or stave off AD (e.g., turmeric curcumin, an anti-inflammatory, anti-amyloid, and anti-tau supplement for brain areas that control mood and memory).

Alzheimer is not a single disease

Strictly speaking, and contrary to medical dogma, AD is not a single disease. There actually are three (not one) distinguishable syndromes (or subtypes of AD: # 1, # 2, # 3). These are inflammatory, neurotrophic (shortage of brain-boosting nutrients, hormones, and other cognition-supporting molecules), and toxic (including glycotoxic) exposure (acronym INT). Each subtype is driven by different biochemical processes, requiring a different treatment. AD can exist in either one or often a combination of such subtypes.

The potential therapeutic effect of the amyloid peptide in the AD has only been demonstrated in mouse and worm models.[5-7] On autopsy, brains of patients who had died of AD, more and more scientific evidence is pointing to the conclusion that after a brain is invaded by pathogens (bacteria from the mouth, molds from the nose, and viruses such as Herpes from the lips, Borrelia [the Lyme disease organism] from a tick bite), they produce Aβ, a potential pathogen fighter, but one that eventually goes overboard, killing the very synapses and brain cells the amyloid was called on to protect.

Alzheimer can be prevented, delayed, reversed, or cured

AD can be prevented, delayed, reversed and even cured depending on a person's individual genetic inheritance, present metabolism, and historical and lifestyle factors. The reason for this statement is that we now have a rational molecular picture of what AD actually is so that we should not be treating the symptoms but the cause(s).

What is Alzheimer's underlying process?

The underlying disease process has typically been ongoing for 15–20 years before a diagnosis is made. The symptoms can be some or all of the following: "Facial blindness (prosopagnosia), decreasing mental clarity (especially later in the day), decreasing interest in reading, an inability to follow or engage in complex conversations, an inability to follow movies with complicated plots, decreasing ability to recall what has been read or heard, decreasing vocabulary, mixing-up words, decreasing processing speed, increasing anxiety about driving and finding one's way, difficulty remembering one's to-do list and appointments and often feeling "overwhelmed" by what needed to be done, sleep disruption, no longer getting a mental boost from caffeine,

and trouble speaking foreign languages known before" (2, pp 32-5).

Clinically, the AD is a state of imbalance between the reorganization of synapses that have outlived their usefulness and should be discarded (but may not have been) and the maintenance of existing synapses or the creation of new ones.

Why have all pivotal clinical trials for experimental Alzheimer's drugs failed?

All pivotal clinical trials for experimental Alzheimer's drugs have failed because they have been designed to address only one or a few of the risk factors. Further, as clearly stated by Professor Gary Small, a UCLA Professor of Psychiatry: "*Although many of the anti-amyloid treatments have been shown to reduce accumulation in the brain, they have yet to demonstrate a benefit for memory loss and other cognitive symptoms that characterize the disease*." (Mind Health Report, November 2017).

How to prevent, delay, minimize, or reverse Alzheimer's?

The first step in preventing, delaying, minimizing, or reversing AD consists in identifying which of the many potential contributors to the three AD subtypes a patient's brain responds to defensively. The second step is to minimize or better remove as many of these contributors as possible. The next step is to remove the amyloid itself. The last step is to help the brain fend off the remaining attackers by rebuilding the synapses that the disease had destroyed.

Addressing the various neuro threats

The basics of addressing each neuro threat are:

1. Prevent and reduce inflammation: Inflammation can be caused by infections (acute or chronic, and sterile), including inflammation-inducing foods and non-infectious stresses (such as sugar-damaged proteins or trans fats). In the former case, to fend off invading pathogens (viruses, bacteria, fungi, and parasites), the brain responds by producing Aβ. The problem arises when the inflammation is chronic, triggering a continuously activated inflammatory response. When the inflammation is caused by sugar toxicity, it is typically accompanied by insulin resistance. This is combated by the insulin-degrading enzyme (IDE). IDE has the dual role of both combating the excess insulin and removing the Aβ. This dual role cannot be played equally in both instances; thus, combating excessive insulin is to the detriment of eliminating Aβ. The answer to the inflammation problem is multi-pronged: (a) Address potential infections, (b) optimize the immune system's ability to destroy pathogens, and (c) reduce chronic inflammation.
2. Optimize neurotrophic factors, including hormones: This strengthens synapses. Among the synapse-strengthening compounds are brain-derived neurotrophic factors (BDNF), which can be increased through exercise, hormones (estradiol and testosterone), Vitamin D, and folate (vitamin B_9).
3. Eliminate toxins: Particularly toxic metals (copper and mercury) and biotoxins (mycotoxins produced by molds). Detoxification includes, among other things, consuming detoxifying foods (e.g. cruciferous vegetables), hydrating with pure-water, and increasing certain molecules (such as glutathione).

BIOCHEMICAL MARKERS

Table 1 lists the biochemical markers of the three subtypes of AD.

THE GOLD STANDARD EVALUATION FOR ALZHEIMER'S DIAGNOSIS

This is summarized in Table 2. It is only after such testing that a proper diagnosis can be made and the corresponding medication(s), if any, could be prescribed (The notes after the end of the table follow the same numbering system as the risk factors).

ASSESSING THE GENETIC AND BIOCHEMICAL STATUS, AND HISTORICAL AND LIFESTYLE FACTORS

For each individual, the following tests give a personalized risk profile. However, depending on the condition of the patient, the number of suboptimal test results will vary.

Tests of genetic and current biochemical condition

As for any therapeutic program, it is important to determine a person's genetic inheritance and biochemical status. For this purpose, the tests described in Table 3 are needed (Entries in Table 3 have been synthesized, adapted and augmented from data in[2]). There are seven categories including several sub-categories of tests: (a) Genetic, (b) blood, (c) trophic support, (d) leakage, (e) toxicity, (f) cognitive performance, and (g) others (imaging, sleep, microbiome, mitochondrial function, and body mass index), and related considerations of (h) patient's family history and lifestyle. The critical (and also the optional) tests are listed including the target values, the reasons for performing the tests, and some associated comments (The notes after the end of the table follow the same numbering system as the risk factors). These tests will pinpoint which factors are driving cognitive decline, be it SCI, MCI, or any stage of AD.

Table 1: Biochemical markers of the three subtypes of AD

Subtype #	Biochemical markers	Notes
1. Inflammatory 2XApoE4 (quickest response to treatment)	1. Increased C-reactive protein 2. Decreased (albumin: globulin) ratio 3. Increased IL-6 4. Increased TNF 5. Abnormal metabolism and hormones 6. Increased homocysteine	1. A measure of inflammation caused by infectious agents (bacteria, viruses, and fungi), radicals, AGE products, trauma, damaged proteins, damaged lipids (ox-LDL), etc. 2. Albumin is a key blood protein; globulin is a catchall name for~60 blood proteins 3. IL-6 rises with inflammation 4. TNF (another protein) rises with inflammation 5. Insulin resistance 6. Like in subtype # 2
2. Neurotrophic 1 or 2XApoE4 (slower response to treatment)	1. Sub-optimal hormones levels 2. Reduced vitamin D 3. Insulin resistance 4. Increased homocysteine	
3. Toxic 1XApoE3	1. Atrophied brain regions 2. Neuroinflammation and vascular leak 3. (Zinc: copper) ratio much higher than 1 4. Frontotemporal depression or abnormal AD 5. Hormonal abnormalities 6. Heavy metal (copper and mercury) and biotoxin (e.g., molds) levels	1. Evidenced by MRI 2. Evidenced by MRI 3. Abnormal PET 5. A dysfunctional HPA (Hypthalamus+Pituitary gland+Adrenal gland)-axis shows in blood tests as: low cortisol, high reverse T3 (thyroid test), low free T3, low pregnenolone, low estradiol, low testosterone, other hormonal abnormalities
Glycotoxic	1. High glucose 2. High insulin	1. Causes glycation and inflammation 2. Results in insulin resistance

Source: Synthesized, adapted and augmented from Reference (2). IL-6: Interleukin-6, TNF: Tumor necrosis factor, AGE: Advanced glycation end products, LDL: Low-density lipoprotein, AD: Alzheimer's disease, MRI: Magnetic resonance imaging, PET: Positron emission tomography, APoE: Apolipoprotein E

While laboratory tests are important for identifying genetic and biochemical factors that may be contributing to cognitive decline, historical, and lifestyle factors may also contribute significant factors and information. These other considerations are summarized below.

OPTIMIZING ALL OFFENDING BIOCHEMICAL TEST RESULTS

Reducing the Aβ plaques is unlikely to help for this does not address the root cause of the problem, just the response to it. What will help is identifying the inducers of the plaques' production and removing them following priority order. While remaining within the guidelines within each test is helpful, the goal is to go beyond and optimize the test values in as many categories as possible.

DETERMINING WHICH ALZHEIMER SUBTYPE OR COMBINATION APPLIES

The three types of the AD (acronym INT) may apply either singly or in combination. They are, again:

1. "Inflammatory": This is part of the reaction of the immune system to foreign invaders. It is woven in our genes (like cancer). As we age, inflammation promotes cardiovascular disease, arthritis, and many other ailments, not to mention aging itself. (This is called "antagonistic pleiotropy," a trade-off in which a genetic alteration enhances fitness early in life at the expense of longevity). ApoE is the most important of all inflammatory genes. It can be counteracted with fish oil, baby aspirin, and anti-inflammatory diets;
2. "Neurotrophic"(nutrition and metabolism of tissues under nervous influence); and

Table 2: The gold standard evaluation for a diagnosis of Alzheimer's disease

Item	Remarks
0. Rule out brain tumor	From an MRI or PET scan
1. Genetics	ApoE status and dozens of other genes that raise risk for AD. Risk depends on the gene ApoE-4, which is associated with a higher risk of developing AD. The ApoE gene produces a protein that transports cholesterol into brain cells
2. Inflammation	A key player
3. Infections	Bacteria (P. gingivalis), viruses (Herpes simplex-1, Lyme) various fungi, and others
4. Homocysteine	An amino-acid causally associated with AD and brain atrophy
5. Fasting insulin level	Inflammatory response caused by sugar toxicity
6. Hormonal status	Estradiol testosterone, thyroid-stimulating hormone, etc.
7. Toxic exposure	Mercury, mycotoxins, etc.
8. Immune system (particularly, the innate part)	Responds first to infections
9. Microbiome	Bacteria and other microbes living in the gut, mouth, nose, and sinuses
10. Blood-brain barrier	Impaired integrity allows access to the brain by microbes, viruses, fungi, etc.
11. Body mass index	Measure of an overweight condition
12. Diabetes or pre-diabetes status	Drivers of AD
13. Volumetrics	Subtype # 3: generalized brain atrophy; Subtypes # 1 and # 2: hippocampal atrophy

Source: Synthesized, adapted and augmented from Reference (2). (1) There are three types of ApoE: ApoE2, 3, and 4, each with 1 or 2 variants (alleles). Most people carry two alleles of ApoE3 (one from the father and one from the mother) leading to an AD risk of~9%. Those who carry a single copy of ApoE4 have an AD risk of~30%, and those who carry two copies of ApoE4 have a risk well above 50%, that is, will develop AD (but not always) through the inflammatory subtype. The ApoE effects are: (a) To increase the risk of AD because it reduces the clearance of the Aβ peptides; (b) it enters the nucleus and binds very efficiently to DNA, thus reprogramming cells; (c) it is involved in 17,000 genes out of a total of 20,000 genes in the entire human genome, thus also playing a role in cardiovascular disease, inflammation, and more. The ages of onset of AD are typically: For ApoE4 (2 alleles): 40s-50s; for ApoE4 (1 allele): late 50s–60s; and for no copies of ApoE4: 60s–70s. People who have high cholesterol or heart disease are more sensitive to the gene's negative cognitive effects. (2) Other genes: presenilin-1, 2 (PS1, 2) also increase the risk of the AD. They account for<5% of cases. AD: Alzheimer's disease, MRI: Magnetic resonance imaging, PET: Positron emission tomography, ApoE: Apolipoprotein E

Table 3a: Tests needed for assessing a person's risk for Alzheimer's disease: Genetic tests

Critical test (s)	Target values	Optional test (s)	Reason (s)	Comments
Genetics				
ApoE	Negative for ApoE4	Whole genome, Exome, SNPs (including APP, PS1, PS2, CD33, TREM2, CRI, NLRP1)	Strongest known risk factor	Test by "23andMe" from saliva or blood, to be followed by analysis from (www.promethease.com)
(Loss of Y-chromosome)			Escalates the risk by a factor of~7	Still in early research

(1) There are three types of ApoE: ApoE2, 3, and 4, each with 1 or 2 variants (alleles). Most people carry two alleles of ApoE3 (one from the father and one from the mother) leading to an AD risk of~9%. Those who carry a single copy of ApoE4 have an AD risk of~30%, and those who carry two copies of ApoE4 have a risk well above 50%, that is, will develop AD (but not always) through the inflammatory subtype. The ApoE effects are: (a) To increase the risk of AD because it reduces the clearance of the Aβ peptides; (b) it enters the nucleus and binds very efficiently to DNA, thus reprogramming cells; (c) it is involved in 17,000 genes out of a total of 20,000 genes in the entire human genome, thus also playing a role in cardiovascular disease, inflammation, and more. The ages of onset of the AD are typically: For ApoE4 (2 alleles): 40s–50s; for ApoE4 (1 allele): late 50s–60s; and for no copies of ApoE4: 60s–70s. People who have high cholesterol or heart disease are more sensitive to the gene's negative cognitive effects. (2) The escalated risk is consistent with other work indicating a link between an altered immune system and AD. Researchers have speculated that loss of genes on the Y - chromosome may make immune blood cells dysfunctional, rendering them unable to stave off the disease. APoE: Apolipoprotein E, SNP: Single nucleotide polymorphism, APP: Amyloid precursor protein, PS1: Gene Presenilin-1, PS2: Gene Presenilin-2

Table 3b: Tests needed for assessing a person's risk for AD: Blood tests

Critical test (s)	Target values	Optional test (s)	Reason (s)	Comments
Blood tests				Tests of inflammation versus cellular protection
hs-CRP (mg/dl)	<0.9	Cytokines: IL-6, TNFα	A marker of inflammation	Standard CRP is too insensitive to distinguish optimal from mildly abnormal. Cytokines coordinate the immune response to inflammation
Homocysteine (μmole/l)	<7 Higher levels cause cognitive decline and hippocampal shrinkage		Important contributor. A marker of inflammation and inadequate nutritional support	a. Comes from foods containing the amino acid methionine b. Can be lowered with MCA (methyl B_{12}), MTHF, and P5P c. Conversion of methionine to homocysteine requires Vitamins B_6, B_9 (folate), and B_{12}
Vitamins: B_1 (nmol/l) B_6 (nmcg/l) B_9 (folate) (ng/ml) B_{12} (pg/ml) C (ng/ml) D_3 (ng/ml) E (mcg/ml)	 Serum: 20–30 or RBC-TPP: 100–150 (ng/ml) 60–100 10–25 500–1,500 1.3–2.5 50–80 12–20	 - High levels toxic to peripheral nerves MMA	 Active forms of B_6, B_9, and B_{12} are required to lower homocysteine Reduced levels are associated with cognitive decline. Essential for creating and maintaining brain synapses	Active forms: Thiamine P5P Methylfolate MMA is complementary Converted from 7-dehydrocholesterol. Measured at 25-hydroxycholecalciferol. Reduces inflammation and maintains brain synapses Measured as α-tocopherol
Omega-6: Omega-3 ratio	0.5–3.0			Omega-6 is pro-inflammatory; Omega-3 is anti-inflammatory
Interleukin-6 (pg/ml)	<3			A cytokine that increases during Type 1 AD (inflammation)
Tumor necrosis factor-alpha (pg/ml)	<6.0			A cytokine that increases during Type 1 AD (inflammation)
Albumin: Globulin ratio	A>4.5 (g/dl) A/G ≤ 1.8			Complementary measure of inflammation
Sugars (g/day) Fasting glucose (mg/dl) Fasting insulin (μIU/ml) Fasting glucose (mg/dl)	<15 70–90 ≤ 4.5 70–90	Neural exosome studies (p-tau, Aβ-42, REST, cathepsin D, IRS-1 phosphate ratio)	High-risk factors Causes inflammation AGE products cause free radicals to form damaging DNA and cell membranes Damages blood vessels thus reducing nutritional support to the brain-derived Causes leakiness of the BBB	Counteracts IDE as it degrades Aβ plaques Produces AGE products that cause inflammation, reduced nutritional support, BBB leakage (Types 1, 3 AD) Measures altered molecules (glucose attached to proteins)

(Contd...)

Table 3b: *(Continued)*

Critical test (s)	Target values	Optional test (s)	Reason (s)	Comments
Hemoglobin A1c (%)	<5.6			A measure of inflammation
Lipoproteins: LDLp, or sdLDL (mg/dl), or oxLDL (U/l) HDL Cholesterol (total) Triglycerides (mg/dl)	 700-1,000<20 or~20% LDLp<60 - >150<150 (=1.7 mmol/dl)		To measure damaged cholesterol (not total cholesterol) along with the degree of inflammation	Vascular disease contributes to cognitive decline Total cholesterol<150 (mg/dl) may lead to brain atrophy
Glutathione (micromolar)	5.0–5.5			A detoxifier. See also selenium, 6.8

(1) Comes from foods containing the amino acid: nuts, meats (beef, lamb, and pork); dairy (cheese); poultry (turkey, eggs); beans; soy. Homocysteine is converted back to methionine or cysteine. (2) It is a marker of inflammation and inadequate nutritional support. Important contributor to AD but also for cardiovascular disease, stroke, and even some cancers (8). (3) – (a) Vitamin B_1 (Thiamine) is critical for memory formation (the Wernicke-Korsakoff syndrome). Unclear role in cognitive decline associated with AD or aging. (b) Vitamin D is provided when sunlight converts a cholesterol molecule (7-dehydrocholesterol) into an inactive form of Vitamin D, which is subsequently converted into the active form. (c) Vitamin E is (a) an important protein for cell membranes and (b) an anti-oxidant with an anti-AD effect. It includes tocopherols and tocotrienols. Even as a monotherapy, can slow cognitive decline, modestly in AD. (4) Fatty acids that are important for health. (5) A cytokine that increases during inflammation. (6) Contributes also to Type 2 diabetes, fatty liver, and metabolic syndrome. While the link of cholesterol to cardiovascular disease is arguably controversial, that to cognitive decline is not. Surprisingly, low rather than high cholesterol is associated with cognitive decline. Vascular dementia is associated with many small strokes. Total cholesterol<150 leads to brain atrophy. AD: Alzheimer's disease, CRP: C-reactive protein, MCA: Methylcobalamin, MTHF: Methyltetrahydrofolate, P5P: Pyridoxal-5-phosphate, RBC: Red blood cell, MMA: Methylmalonic acid, TPP: Thiamine pyrophosphate, IDE: Insulin-degrading enzyme, AGE: Advanced glycation end products, BBB: Blood-brain barrier, DNA: Deoxyribonucleic acid, LDLp: Low-density lipoprotein-particle, LDLsd: Low-density lipoprotein-small dense, LDL-ox: Low-density lipoprotein-oxidized, HDL: High-density lipoprotein

3. "Toxic" (including Glycotoxic).

The results of the various tests and considerations in Tables 3a-h will help determine which AD-subtype(s) or combination thereof applies.

TREATMENT CONCEPTS

The key treatment concepts follow (Table 4).

THE DESS APPROACH

The acronym DESS stands for: Diet, Exercise, Sleep, and Stress, as further discussed below.

Diet

This type of diet increases production of the neuron-supporting molecule BDNF, prevents gut leak, and optimizes the microbiome. Professor Bredesen advocates a modified ketogenic diet, which he dubbed as "Ketoflex 12/3" consisting of three principles:

1. Ketosis: This is the process whereby the liver produces specific chemicals called ketone bodies (acetoacetate, beta-hydroxybutyrate, and acetone) by breaking down fat. Ketosis is promoted by a low-carbohydrate diet, moderate exercise, and fasting (see further discussion in item three below). It switches the metabolism from carbohydrate-burning and insulin resistance, which promotes AD, to fat-burning and insulin sensitivity, which helps prevent it. Mild ketosis is optimal for cognitive function.
2. Flexitarian diet: This is a largely plant-based diet with an emphasis on vegetables (especially non-starchy ones) and a limited consumption of meat.
3. 12/3: This is fasting at least 12 h between the last meal of the evening and the first meal of the next morning (which promotes autophagy, recycling components, destroying damaged proteins and mitochondria, depleting the liver's stores of glycogen, and inducing ketosis), and allowing a minimum time of 3 h between the last meal of the day and bedtime (which helps keep insulin levels from spiking).

For more specifics, the reader is referred to books published on the subject, particularly.[2] (See also the Appendix.) Other helpful diets are: The Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean-DASH Intervention for neurodegenerative delay) diet. The latter eating plan is a combination of a diet for people with high blood pressure and a Mediterranean-style diet. People who follow it have a 35% lower risk for cognitive impairment compared to those who did not.

Exercise

Exercise has the following benefits: Reducing insulin resistance and stress; increasing ketosis, the size of the

Table 3c: Tests needed for assessing a person's risk for Alzheimer's disease: Trophic support status

Critical test (s)	Target values	Optional test (s)	Reason (s)	Comments
Hormonal status			Signaling molecules that contribute crucially to optimal cognitive function by supporting synapse formation and maintenance	Gut-brain connection is critical for cognition
Thyroid Free (active) T_3 (pg/ml) Free (active) T_4 (ng/dl) Reverse T_3 (ng/dl) TSH (micro IU/ml)	 3.2–3.4 1.3–1.8<20<2.0		A measure of metabolic speed (heart rate, mental sharpness)	Many people with dementia, SCI, MCI have suboptimal thyroid function 100 free T3/free T_4>$_{20}$
Estrogens (estradiol. estriol, estrone) (pg/ml)	50–250			Crucial in prevention of dementia
Progesterone (ng/ml)	1-20			Controversial role in cognitive function
Testosterone (ng/dl) Total Free	 500–1,000 6.5–15			Men at lowest quintile are at increased risk of AD
Cortisol (mcg/dl)	10–18		Chronic stress contributes to hippocampal damage and thereby cognitive decline	Rapid reduction leads to loss of neurons in the hippocampus
Pregnenolone (ng/dl)	50–100		Risk factor for cognitive decline	
DHEA (mcg/dl)	Women: 350–430 Men: 400–500			

(1) Also affects reflexes, length of sleep, whether one feels cold or hot, gains weight easily, becomes depressed, and many other health parameters. (2) While playing a controversial role in cognitive function, it is crucial in preventing dementia. (3) A high value of the ratio (estradiol: progesterone) is associated with "brain fog" and poor memory. (4) Synthetic testosterone injections to raise testosterone levels may increase risk for prostate cancer. (5) Stress activates the HPA axis. The brain's hypothalamus produces CRF, which stimulates the pituitary gland to release ACTH into the blood that, in turn, causes the adrenal glands atop the kidneys to release cortisol and other stress-related hormones. (6) This is the master steroid hormone. Supports memory and is neuroprotective. (7) A "neurosteroid" that supports response to stress. TSH: Thyroid-stimulating hormone, SCI: Subjective cognitive impairment, MCI: Mild cognitive impairment, AD: Alzheimer's disease, DHEA: Dehydroepiandrosterone acid, ACTH: Adrenocorticotropic hormone, HPA: Hypothalamus-pituitary gland-adrenal glands axis, CRF: Corticotropin releasing factor

hippocampus, and the survival of newborn neurons; and improving vascular function, sleep, and mood.

Sleep

There are three main reasons for awakening at night: Over-production of serotonin; reduced progesterone (a relaxing hormone; its reduction is associated with anxiety, poor sleep and often "brain fog"); and stress. Common sleep problems are associated with increases in some biomarkers of the AD. For example, people who suffer from obstructive sleep apnea have more amyloid and cerebral spinal fluid in their brains than those who do not have such disorders. Restful sleep actually helps to clear amyloid from the brain and offers an anti-inflammatory benefit, which can further boost brain health.

Stress

Stress is a factor in most cases of cognitive decline. It increases the levels of cortisol and a number of risk factors for cognitive decline and AD (blood glucose level, body fat, risk for obesity, carbohydrate craving, leaky gut, permeability of the BBB, calcium release, hyperstimulation of neurons, and risk of cardiovascular disease). It also attacks factors that protect against AD.

APPROACH TO A TARGETED PERSONALIZED TREATMENT

Professor Bredesen and his team have developed a targeted, personalized program, called for reversing cognitive decline, which they claim has succeeded in preventing and reversing the cognitive decline of dementia. For specific details of this program, the reader is referred to.[2]

Table 3d: Tests needed for assessing a person's risk for AD: Leakage tests

Critical test (s)	Target values	Optional test (s)	Reason (s)	Comments
Leakage tests				
Leaky gut	Negative	Cyrex array #2 #3 (for antibodies) #4 (for rye, barley, sesame, oats, rice)		Gut-brain connection is critical for cognition Case of gluten sensitivity
Leaky BBB	Negative	Cyrex Array #20		*Porphyromonas gingivalis, Fusobacterium nucleatum, Prevotella intermedia*. HSV, neurosyphyllis, Lyme disease, etc.
Gluten sensitivity	Negative	Tissue transglutaminase antibodies negative; or Cyrex Array #3 and #4		
Autoantibodies	Negative	Cyrex Array #5		

(1) Contributes to inflammation and other conditions. Causes yeast and fragments thereof to enter the bloodstream. May cause persistent low-level inflammation, autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, lupus erythematosus. Chronic inflammation contributes to AD. (2) BBB porosity can produce mild, chronic inflammatory response associated with AD.[9-12] (3) Gluten sensitivity can trigger chronic inflammation that leads to AD. AD: Alzheimer's disease, BBB: Blood-brain barrier

SUMMARY AND CONCLUSIONS

Professors Dean and Ayela Sherzai of the Loma Linda University Medical center have advocated similar principles and diet program. Contrary to prevailing medical dogma, the formation of amyloid-beta plaques is not the cause of AD, but the normal brain's immune response to several neuro threats. Further, AD and the associated cognitive decline of dementia are curable and can be prevented, minimized and even reversed. Whether the formation in the brain of amyloid-beta and its accumulation in sticky, synapse-destroying plaques is the cause of the disease or merely a component of it, or else, the normal brain response to insults remains an issue. Another issue is whether AD is a single disease type or three distinct subtypes, or a combination thereof, each requiring a separate treatment. The above assertions have been reviewed beginning with our current knowledge of AD. It was explained why the presently approved drugs have at best been of limited palliative effect. These drugs are monotherapies in a complex disease involving multiple neuro threats (~36–40, or perhaps slightly more). The several neuro threats have been addressed, and the known biochemical markers and corresponding genetic and biomedical tests have been analyzed in addition to associated historical and lifestyle factors. Most such tests are needed to assess the status of any given AD individual so as to devise an appropriate and effective individualized treatment. The combination (diet, exercise, stress, and sleep) is a recipe for the potential end of the AD. The Appendix has discussed briefly the ketogenic diet and several of its variants.

Abbreviations

αCTF=(a peptide); Aβ=Amyloid-beta (a peptide); ACTH=AdenoCorticoTropic Hormone; AD=Alzheimer's Disease; ADAM10=Enzyme Alpha-Secretase; AGE=Advanced Glycation End products; AHI=Apnea-Hypoapnea Index; ApoE=ApolipoproteinE (a genetic marker for AD); APP=Amyloid Precursor Protein (a dependance receptor); ATP=Adenoid Tri-Phosphate; AZT=Azidothymidine; BBB=Blood Brain Barrier; BDNF=Brain-Derived Neurotrophic Factor (a neuron-supporting molecule); BMI=Body Mass Index; CAT=Computer Assisted Tomography; CBC=Complete Blood Count; CIRS=Chronic Inflammatory Response Syndrome; CRF=Corticoprotein Releasing Factor; CRP=C-Reactive Protein (an inflammation marker); CVD=CardioVascular Disease; DASH=Dietary Approaches to Stop Hypertension; DESS=Diet, Exercise, Sleep, Stress reduction; DHEA=DeHydroEpiandrosterone Acid; DNAS=DeoxyriboNucleic Acid; FDA (U.S. Food & Drug Administration); FLAIR=Fluid Attenuated Inversion Recovery (an MRI image reconstruction technique); FTD=FrontoTemporal Dementia; GI=Gastro-Intestinal; GI=Glycemic Index; GSH=Glutathione. HDL=High Density Lipoprotein; HIV/AIDS: Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; HSV=Herpes Simplex Virus; HPA=Hypothalamus-Pituitary gland-Adrenal glands axis; hsCRP=high sensitivity CRP; IDE=Insulin-Degrading Enzyme; IDEAS=Imaging Dementia Evidence for Amyloid Scanning; IGNT=Inflammatory- Glycotoxic-Neurotrophic-Toxic (acronym for a PD theory); IL-6=Inter-Leukin-6; LBD=Lewy Body Dementia; LDL=Low Density Lipoprotein; LC=Long-Chain Carbohydrates; LDL-ox=LDL-oxidized; LDL-p=LDL-particle; LDL-sd=LDL-small dense; LD=Lyme Disease; MAD=Modified Atkins Diet; MCA=Methylcobalamin; MCC=Medium-Chain Carbohydrates; MCI=Mild Cognitive Impairment; MIND=Mediterranean-DASH Intervention for

Table 3e: Tests needed for assessing a person's risk for AD: Toxicity tests

Critical test (s)	Target values	Optional test (s)	Reason (s)	Comments
Toxins related				
Heavy metals Arsenic (mcg/l) Cadmium (mcg/l) Lead (mcg/l) Mercury (mcg/l)	 <7<2.5<2 <5	For all: Quicksilver test: <50th percentile		Impairs executive functioning, reduces mental acuity depression - Impairs cognitive function Induces amyloid beta plaques and neurofibrillary tangles. Destroys part of glutathione
(Copper: Zinc)-ratio	0.8–1.2	RBC zinc, ceruloplasmin	Too much copper and too little zinc are associated with dementia	
Mycotoxins: C4a (ng/ml) TGF-β1 (pg/ml) MSH (pg/ml)	 <2,830<2,380 35–8.1	MMP9, VEGF, ADH, osmolality Urinary mycotoxin test		If abnormal, add: MARCoNS culture and VCS testing Negative for trichothecenes, ochratoxin A, aflatoxin, gliotoxin derivative
HLA-DR/DQ	Benign			No propensity for CIRS
Other metals and molecules				
RBC magnesium (mg/dl) RBC zinc (mg/l)	5.2–6.5 12–14			Critical for brain function. RBC measurements are more accurate than in serum
Copper (mcg/dl) Zinc (mcg/dl)	90–110 90–110		(Copper: zinc)-ratio=0.8–1.2; ≥1.4 associated with dementia	Additional optional target: (Copper-3) X Ceruloplasmin ≤30
Selenium (ng/ml)	110–150			Works with the peptide glutathione to mop-up free radicals. Reductions are associated with cognitive decline
Glutathione (micromolar)	5.0–5.5			See 2.11
Potassium	4.5–5.5			
Calcium	8.5–10.5			

(1) Arsenic leads to age-related cognitive decline. (2) Cadmium acts with lead and arsenic to enhance AD's changes in the brain. (3) Lead. (4) Mercury poisoning leads to: (a) Memory loss, (b) depression, (c) insomnia, (d) tremors, (e) irritability, (f) extreme social phobia, and (g) induces Aβ plaques and neurofibrillary tangles. Arsenic leads to (a) impaired executive function, (b) reduced mental acuity, (c) deterioration of verbal skills, and (d) depression (typical of AD-type # 3). Quicksilver Scientific offers sensitive blood tests for: Aluminum, antimony, arsenic, barium, cadmium, calcium, chromium, cobalt, copper, lead, lithium, magnesium, mercury, molybdenum, selenium, silver, strontium, titanium, and zinc, (1) Molds (*Stachybotrys, Aspergillus, Penicillium*, and *Chaetomium*) cause CIRS. (2) Pairing magnesium supplements with the amino acid threonine improve cognitive function. (3) Low zinc levels are associated with: (a) aging; (b) AD subtype 3, which causes sensitivity to toxic metals (e.g., mercury) and mycotoxins (from molds); (c) increased level of autoantibodies, a source of inflammation; (d) increased oxidative damage and aging; (e) reduced hormonal signaling and neurotransmitter signaling; and (f) increased sensitivity to toxins. (a)-(f) Are characteristics of AD subtype 3. Zinc is also critical for insulin synthesis, storage. Zinc supplements enhance cognition. Copper (but not zinc) is a source of free radicals. (4) Works in pair with glutathione. Plays a key role in generating glutathione. (5) Works in pair with selenium. Low levels contribute to inflammation, toxicity, and loss of support for synapses (affects all AD subtypes). AD: Alzheimer's disease, RBC: Red blood cell, TGF: Transforming growth factor, MSH: Melanocyte-stimulating hormone, VEGF: Vascular endothelial growth factor, ADH: Antidiuretic hormone, CRIS: Chronic inflammatory response syndrome

Table 3f: Tests needed for assessing a person's risk for AD: Cognitive performance tests

Critical test (s)	Target values	Optional test (s)	Reason (s)	Comments
Cognitive performance				
Quantitative neuropsychological (brain HQ, or equivalent) MoCA test score (26–39)	>50th percentile for age 19–25: MCI 19–22: MCI with daily living difficulties<19: dementia	Novel object recognition	To know where one stands with memory and other aspects of cognition	Improving with practice

Other simple tests include MMSE, SAGE, CNS Vital Signs, Brain HQ, Dakim, Lumosity, and Cogstate. MCI: Mild cognitive impairment, MMSE: Mini-mental state examination, SAGE: Self-administered gerocognitive examination, CNS: Central nervous system, MoCA: Montreal cognitive assessment test, AD: Alzheimer's disease

Table 3g: Tests needed for assessing a person's risk for AD: Other tests

Critical test (s)	Target values	Optional test (s)	Reason (s)	Comments
Imaging				
Brain imaging	MRI with volumetrics showing areas of atrophy	Hippocampal, cortical volume percentiles (steady or increasing) for age: >25th percentile CSF spinal tap		NeuroReader or NeuroQuant software programs for % scoring To distinguish frontotemporal dementia and AD
Neural exosomes	Normal levels of amyloid-beta 42, phospho-tau, cathepsin D, REST, Phosphorylation ratio of IRS-1			Novel test can determine many chemical signatures of the brain and which AD subtype applies
Retinal imaging	Negative for plaques			Novel test
PET FDG-PET Amyloid-PET Tau-PET	Negative Negative Negative Negative			
Object recognition	Normal preference for novel objects	Neurotrack's ICAT test	Detects impairment of the hippocampus and nearby structures	
EEG	Normal			No seizure activity or slowing
Sleep				
Sleep study	AHI<5/h			Preferably AHI=0/hour
Microbiomes				
Gut Oral Nasal	No pathogens			
Mitochondrial function	No exposure to damaging agents			Case of significant amounts over long periods of time

(Contd...)

Table 3g: *(Continued)*

Critical test (s)	Target values	Optional test (s)	Reason (s)	Comments
Others				
BMI	18-25			Waistline: <35 in (women), <40 (men)
Blood test for amyloid accumulation			Less invasive, cheaper	A novel blood biomarker under testing

(1) Neural exosomes are tiny fragments of cells' detritus and secretions that are excreted in the blood. A blood test for exosomes can determine many critical parameters of brain chemistry. May show increases in amyloid beta, phosphorylated tau, and insulin resistance. Has the potential to assess neurotransmitter pathways, hormonal signaling, trophic factor signaling, vitamins effects on neural function, trauma effects, vascular compromise, therapeutic responses, and many more chemical signatures in the brain. (3) Retinal imaging can identify many small plaques (smaller than with PET), map the location of each, and follow-up after treatment. (4) The ongoing IDEAS Study is evaluating whether obtaining a PET scan has an effect on a patient's clinical outcome. These scans display levels of brain amyloid. Results suggest that amyloid PET scans alter patient management. A more important outcome would be to determine if the use of the scans resulted in improved outcomes. (5) Sleep affects cognition by (a) altering the cellular anatomy of the brain, (b) associating with a reduced formation of the amyloid, (c) fasting (during sleep) improves insulin sensitivity, (d) during sleep, brain cells activate autophagy, and (e) sleep is a time of repair. Sleep deprivation (a) impairs cognition, (b) increases the risk of obesity, (c) increases the risk of diabetes, and (d) cardiovascular disease (all risks for AD), and (e) improves insulin sensitivity (through fasting during sleep). (6) Mitochondrial damaging agents include antibiotics, statins, alcohol, L-Dopa (against Parkinson's disease), griseofulvin (against fungal infections), acetaminophen (Tylenol), NSAIDs (Ibuprofen, aspirin, and related drugs), cocaine, methamphetamine, AZT (AzidoThymidine used against viral infections including HIV/AIDS). ApoE4 may also be associated with mitochondrial damage. (7) Being developed by the Washington University School of Medicine. MRI: Magnetic resonance imaging, CSF: Cerebrospinal fluid, AD: Alzheimer's disease, PET: Positron emission tomography, FDG: Fluorodeoxyglucose-positron emission tomography, AHI: Apnea-hypopnea index, BMI: Body mass index, APoE: Apolipoprotein E, NSAIDs: Nonsteroidal anti-inflammatory drugs

Table 3h: Tests needed for assessing a person's risk for AD: Historical and lifestyle considerations

History	Diet	Lifestyle
Head trauma	Eat high mercury fish (tuna, swordfish, orange roughy, shark)	Use (d) street drugs
General anesthesia (how many?)	Consume hot-pressed oils (e.g., palm oil)	Drink alcohol (how much?)
Dental (mercury-based) amalgams	Eat foods high in trans fats or simple carbohydrates	Smoke cigarettes
Medications (antidepressants; antihistamines; benzodiazepines Valium; blood pressure pills; protein pump inhibitors; statins)	Eat processed foods or inorganic foods	Have mold in house, car, or workplace
Good oral hygiene practice	Do not drink enough purified water	Use makeup, hair-spray, or antiperspirant
surgical implants		
Liver, kidney, lung, or heart disease		
Snoring		
Chronic sinus problems		
Gastrointestinal problems		
Tick bites (>70 different pathogens)		
Little sweat		
Constipation		

AD: Alzheimer's disease

Neurodegenerative Delay; MMA=MethylMalonic Acid (a complementary test of vitamin B_{12}; MMSE= Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment test; MRI=Magnetic Resonance Imaging (an imaging technique); MTHF= Methyltetrahydrofolate; NeKB=an inflammatory molecule; Netrin-1=a molecule; NIH=U.S. National Institutes of Health; NSAID: Non-Steroidal Anti-Inflammatory Drug; NTR=NeuroTrophin Receptor (a common

Table 4: Key treatment concepts for Alzheimer's disease

Concept	Reason (s)
Begin treatment as early as possible	The earlier the treatment, the greater the chances of success
Address as many abnormalities as possible	Increased chance of success
Optimize each abnormality correction	What may otherwise be considered "normal," may be sub-optimal
For each treatment, address the root cause of the problem targeted	Treating the symptom (s) does not resolve the problem
Iterate on the treatment	The initial treatment must be iterated on to optimize its result
Treatment should not be drug-based	Drugs are not the first line of treatment but can be useful adjuncts
Treatment usually reaches a threshold effect beyond which the pathogenetic process can be halted or reversed	This is similar to other chronic illnesses (cancer, cardiovascular diseases, osteoporosis, etc.)
Lowering sub-optimal homocysteine levels	With active forms of Vitamins B_6 (P5P), B_9 (adenosylcobalamin) (folate), and B_{12} (methyl-B_{12}, typically 20–50, 08–5.9, and 0.5–1.0 (mg), respectively. Follow-up treatment after every 3 months, as needed
Restoring insulin sensitivity and metabolic flexibility	Arguably the single most important metabolic contributors to AD. Critical for trophic factor production, response to trophic effects of insulin, minimizing inflammation, reducing obesity and lipid storage, improving cardiovascular status, optimizing hormones, and thereby enhancing cognition. Solution is an effective combination of diet, exercise, stress, sleep (DESS)

one is p75NTR); PD=Parkinson's Disease; P5P=pyridoxal-5-phosphate; PCD=Programmed Cell Death; PD=Parkinson's Disease; PET=Positron Emission Tomography (a nuclear medicine imaging technique); PPI=Protein Pump Inhibitor; PS1,2=Gene Presinilin-1,2 (genes that increase the risk of AD; they account for less than 5% of cases); RBC=Red Blood Cell; ReCODE=Reversing cognitive decline; REM=Rapid Eye Movement; SAGE=Self-Administered Gerocognition Examination; sAPPα=(a peptide); sAPPβ=(a peptide); sirtuinSurT1=a longevity molecule; SCI=Subjective Cognitive Impairment; SMASH; Salmon, Mackerel, Anchovies, Sardines, Herring; SNP=Single Nucleotide Polymorphism; T3=(a thyroid test); TCM: Traditional Chinese Medicine; TNF=Tumor Necrosis Factor (a protein that rises with inflammation); TPP=Thiamine PyroPhosphate; TRH=Thyroytopin Releasing Hormone; TSH=Thyroid Stimulating Hormone; UARS=Upper Airway Resistance Syndrome; VD=Vascular Dementia.

Drugs cited

Anti-depressants; Anti-histamines; Benzodiazepine (Valium); Blood pressure pills; Donepezil (Aricept - a cholisterase inhibitor); Esomeprazole (Nexium - a protein pump inhibitor); Lansoprazole (Prevacid - a protein pump inhibitor); Memantine (Namenda); Galantamine (Razadyue - a cholisterase inhibitor); Huperzine A (a cholisterase inhibitor); L-Dopa (Levodopa: A drug for PD); Pantoprazole (Protonix - a protein pump inhibitor); Prilosec (a protein pump inhibitor); Rabeprazole (Acipitex - (a protein pump inhibitor); Rivastigmine (Exelon - a cholisterase inhibitor); Statins.

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APPENDIX

THE KETOGENIC DIET AND ITS VARIANTS

There are several variants on the ketogenic diet:

Basic principle

Carbohydrates are converted into glucose, which circulates in the body and provides an important fuel source for brain function. The basic principle of the ketogenic diet is to force the body to burn fats rather than carbohydrates. If there are little carbohydrates in the diet, the liver converts fat into fatty acids and ketones (acetoacetate, beta-hydroxybutyrate, and acetone), which pass into the brain and replace glucose as an energy source. Clinical trials and studies in animal models suggest that ketogenic diets provide neuroprotective and disease-modifying benefits for a number of pediatric and adult neurodegenerative disorders.[13-15]

Classic ketogenic diet

The original ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that was used primarily to treat difficult-to-control (refractory) epilepsy in children. It provides just enough protein for body growth and repair, and sufficient calories to maintain the correct weight for age and height. The effect has been to reduce by half the number of seizures, even after discontinuing the diet. For epileptic adults, a less strict regimen (such as a modified Atkins diet) is similarly effective. However, because of its side effects (constipation, the risk of developing kidney stones), this diet is no longer considered beneficial since the advent and availability of anticonvulsants. The classic ketogenic diet contains a 4:1 ratio by weight of fat to combined protein and carbohydrate. This is achieved by excluding high-carbohydrate foods such as starchy fruits and vegetables, bread, pasta, grains, and sugar while increasing the consumption of foods high in fat such as nuts, cream, and butter. The ketogenic diet or some of its variants was also under investigation for the treatment of a wide variety of neurological disorders other than epilepsy.

Variants of the ketogenic diet

There are several variants of the classic ketogenic diet, which at times have been employed in combination with the classic one:

1. The ketoflex 12/3 diet: It incorporates some daily fasting to the ketogenic diet to benefit from the advantages of both.
2. The medium chain triglycerides (MCTs) variant: Most dietary fat is made of molecules called long-chain triglycerides (LCTs). However, medium-chain triglycerides (MCTs) - made from fatty acids with shorter carbon chains than LCTs - are more ketogenic. They produce more ketone bodies per unit of energy than LCTs. The ketone bodies are produced by the liver in otherwise healthy people when they were starved or if they consumed a very low-carbohydrate, high-fat diet. MCTs are more efficiently absorbed and are rapidly transported to the liver. This variant on a diet uses a form of coconut oil, which is rich in MCTs, to provide around half the calories. As less overall fat is needed, a greater proportion of carbohydrate (as much as 3 times) and protein can be consumed, allowing a greater variety of food choices.
3. The modified Atkins diet (MAD): The original Atkins diet was modified by removing its aim of achieving weight loss. It is a less restrictive variant in use, particularly among older children and adults. It increases the diet's induction phase to control seizures and encourages fat consumption. Compared with the ketogenic diet, the MAD diet places no limit on calories or protein, and the lower overall ketogenic ratio (approximately 1:1) does not need to be consistently maintained by all meals of the day. The MAD diet does not begin with a fast or with a stay in the hospital and requires less dietitian support than the ketogenic diet. Like the classical ketogenic diet, the MAD diet requires vitamin and mineral supplements and children are carefully and periodically monitored at outpatient clinics.
4. The low glycemic index treatment (LGIT): This diet attempts to achieve the stable blood glucose levels seen in

children on the classic ketogenic diet while using a much less restrictive regimen. The underlying hypothesis is that stable blood glucose may be one of the mechanisms of action involved in the ketogenic diet, which occurs because the absorption of the limited carbohydrates is slowed by the high-fat content. Although it is also a high-fat diet (with approximately 60% calories from fat), the LGIT allows more carbohydrate than either the classic ketogenic diet or the modified Atkins diet (~40–60 g per day). However, the types of carbohydrates consumed are restricted to those that have a low glycemic index (lower than 50). Like MAD, LGIT is initiated and maintained at outpatient clinics and does not require precise weighing of food or intensive dietitian support.

5. Caloric restriction: Obesity is associated with an increased risk of dementia. On imaging studies, this is shown by decreased hippocampal volume and increased white matter hyperintensities - two radiological indicators of pathological brain aging. In contrast, in addition to the well-known effects of fasting on seizure frequency, low dietary energy intake is associated with decreased incidence of Alzheimer's and Parkinson's diseases (New York City cohort), and caloric restriction for 6 months improves biomarkers associated with longevity including reduced fasting insulin levels, body temperature, and DNA damage. Caloric restriction might even reduce disease risk and increase lifespan in normal weight subjects. Beneficial effects on mental health have been reported as well, with improved mood following caloric restriction of obese diabetic patients. To date, however, clinical trials looking at the effects of caloric restrictions on brain aging and neurological diseases have not been performed, and all available information is derived exclusively from animal models.