

Alzheimer's Disease: The New Type 3 Diabetes?

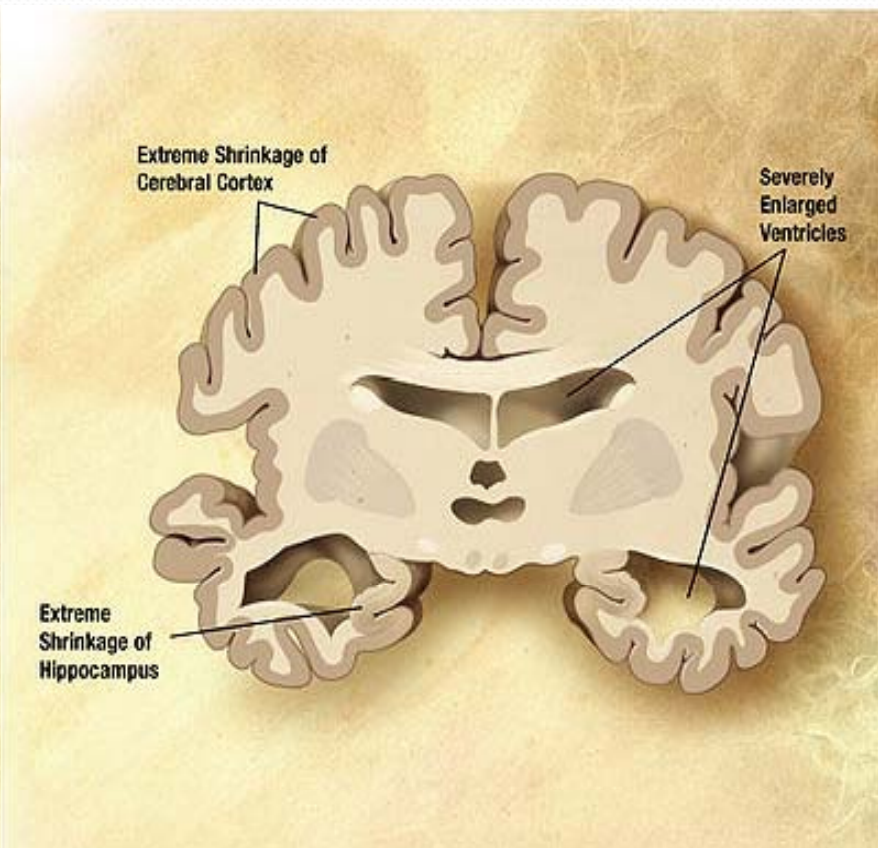
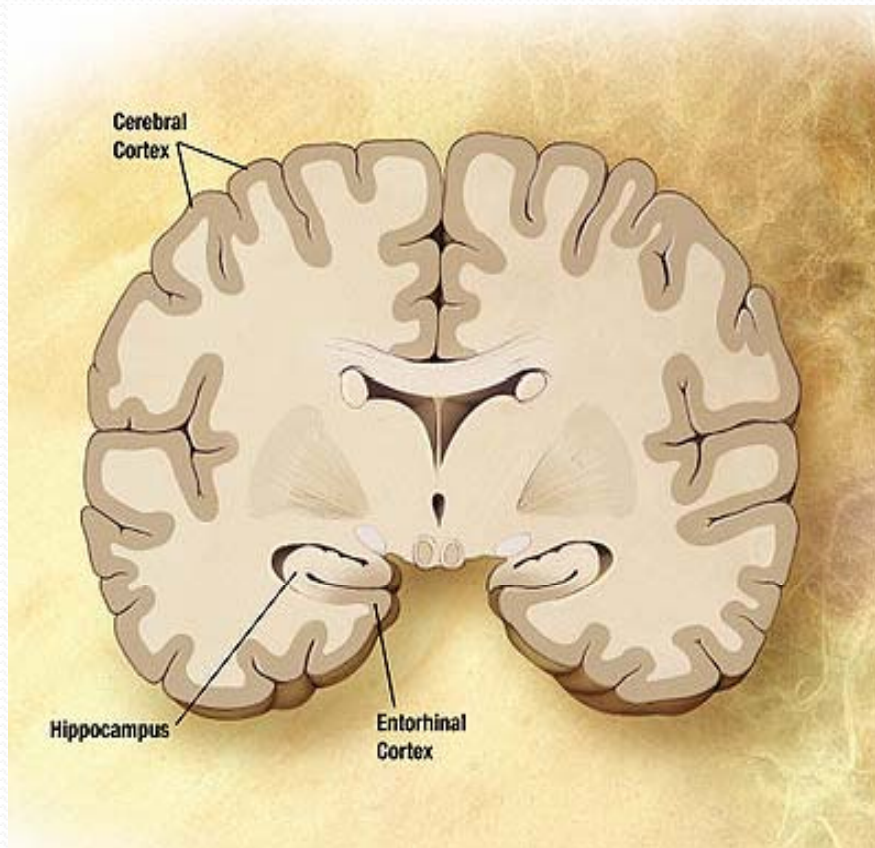


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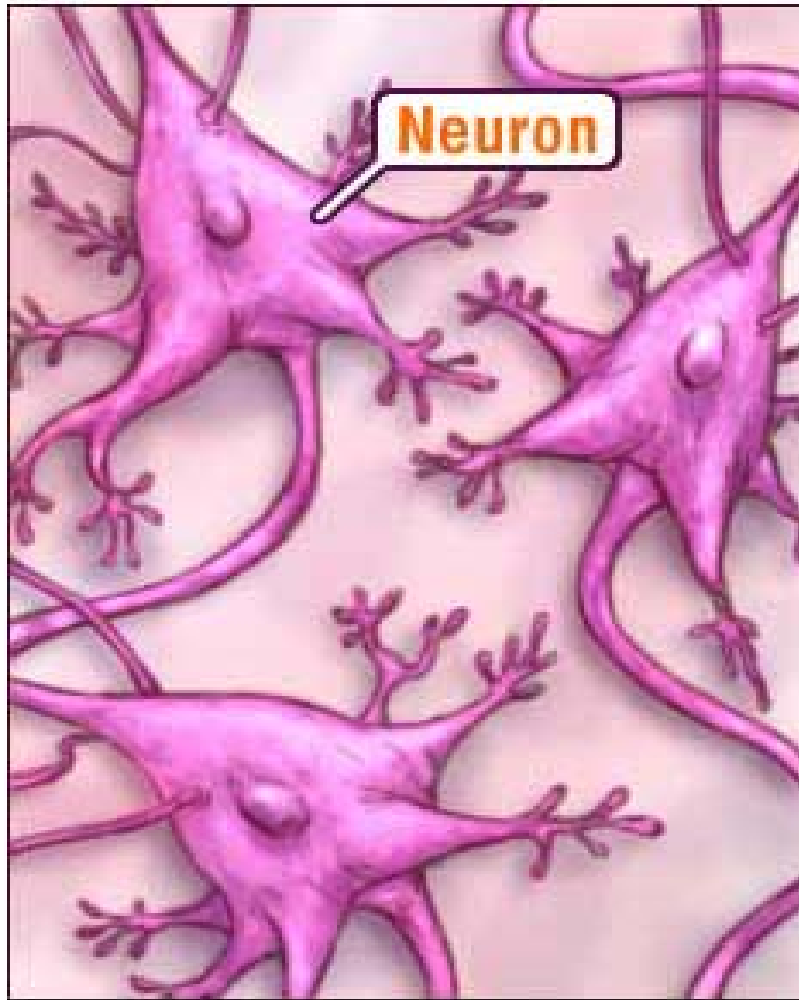
What is Alzheimer's Disease (AD)?

- **Characterized in 1906 by German psychiatrist, Alois Alzheimer**
- **A progressive brain disorder that causes a gradual and irreversible decline in memory, language skills, perception of time and space, emotional stability, pattern recognition, coordination, and, eventually, the ability to care for oneself**
- **Pathology**
 - **Deposits of the protein fragments: beta-amyloid (plaques)**
 - **Twisted strands of the protein tau (tangles); and**
 - **Loss of neurons (brain shrinkage)**

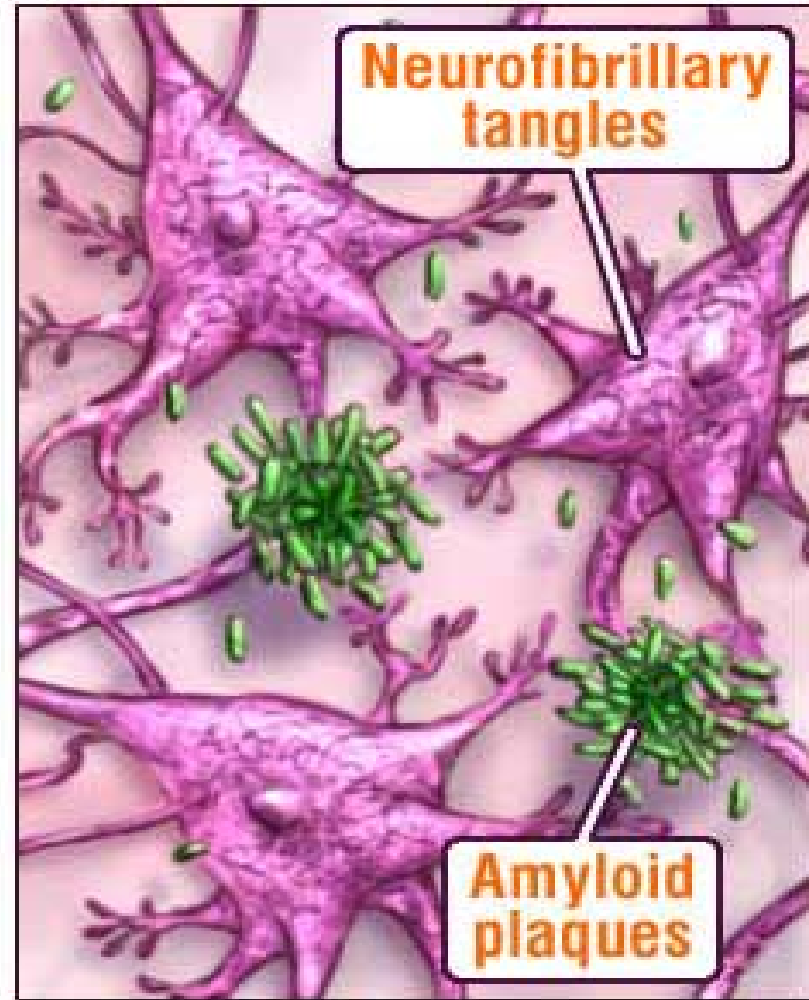
Brain Diagram: Normal vs AD



Normal



Alzheimer's





Symptom Review

- **Early symptoms**
 - **Difficulty remembering names and recent events is often an early clinical symptom**
 - **Apathy and depression are also often early symptoms.**
- **Later symptoms**
 - **Impaired judgment, disorientation, confusion, and behavior changes**
 - **Difficulty speaking, swallowing and walking.**



Alzheimer's Disease: an emerging issue

- **Alzheimer's disease (AD) is the most common form of dementia, accounting for between 70% to over 90% of all cases.**
- **In 2010 an estimated 5.3 million Americans have AD; this number has been projected to increase to 14 million by 2050.**
- **One in eight people aged 65 and older (13 percent) have Alzheimer's disease.**
- **Every 70 seconds, someone in America is diagnosed with AD. By mid-century, it is estimated to be every 33 seconds.**



Alzheimer's Disease: Who is at Risk?

- The greatest risk factor for Alzheimer's disease is advancing age.
 - Most Americans with Alzheimer's disease are aged 65 or older, although individuals younger than age 65 can also develop the disease.
 - As much as 50% of the population aged 85 years and older, the fastest growing segment of the population, may have Alzheimer's disease.



Who is at Risk?

- **More women than men have dementia, primarily because women live longer, on average, than men.**
 - **At age 55, the estimated lifetime risk for Alzheimer's was 17 percent in women (approximately one in six women), compared with 9 percent in men (nearly one in 10 men).**
- **Persons with mild cognitive impairment progress to Alzheimer's disease at the rate of nearly 10% to 15% per year compared to 1 to 2% in elderly persons with normal cognition.**



Who is at Risk?

- **African-Americans and Hispanics are at higher risk for developing Alzheimer's**
 - **African-Americans aged 71 and older are almost two times more likely than whites in the same age group to have Alzheimer's or other dementia.**
 - **21.3 percent of African-Americans compared with 11.2 percent of whites**
 - **Hispanics are about 1.5 times more likely than whites to develop the disease.**
- **Although there appears to be no known genetic factor for these differences, health conditions like high blood pressure and diabetes, conditions that are prevalent in the African-American and Hispanic communities, increase Alzheimer risk.**



Current Treatments: Cholinesterase Inhibitors

- **Donepezil/Aricept sales:**
 - \$1.35 billion in 2004
 - 55% in USA
 - Rose 38% in 2006
- **Neurology Today: 2006**
 - “FDA Approves Donepezil for Severe Dementia. Experts Question Why”

NEUROLOGY TODAY

www.neurotodayonline.com

FDA APPROVES DONEPEZIL FOR SEVERE DEMENTIA – EXPERTS QUESTION WHY

By Stephanie Cajigal

In October, the FDA approved the use of the drug donepezil (Aricept) for patients with severe Alzheimer disease (AD). While more treatment options are usually good news, experts are divided over whether the drug is worth the added effort and cost for patients and families.

The FDA had already approved the drug – a cholinesterase inhibitor – for mild to moderate dementia in 1996, but donepezil is only the second drug after the glutamate modulator memantine (Namenda) approved for severe dementia. The drug's distribution is limited to

patients with severe dementia for six months. Patients were assigned donepezil at 5 mg per day for 30 days, then up to 10 mg per day thereafter, or placebo. Ninety-five patients assigned donepezil and 99 patients assigned placebo completed the study. Primary outcomes were measured using the severe impairment battery (SIB) and the modified Alzheimer's Disease Cooperative Study activities of daily living inventory for severe Alzheimer's disease (ADCS-ADL-severe).

The SIB measures the severity of cogni-

tive dysfunction in advanced AD in terms of memory, language, orientation, praxis, visuospatial construction, ability to name people

and objects, and social interaction. The ADCS-ADL-Severe is a 19-item scale used to measure basic activities of daily living, such as eating and bathing, and complex

abilities, such as opening water taps and switching on lights, with scores ranging from zero to 54. The study defined severe

Continued on page 8



Questions about the cost-effectiveness of donepezil were raised in response to the dearth of data on the quality of life of patients taking the drug.

Cholinesterase Inhibitors

- Review of all published high-quality studies
 - Double blind, placebo controlled, randomized trials
 - Cholinesterase inhibitors for Patients with Alzheimer's Disease: Systematic review of randomized clinical trials. Kaduszkiewicz et al. BMJ on Neurology. 1: 15-21. Fall 2005
- Examined efficacy of these medications on basis of clinical outcomes
 - Donepezil/Aricept, rivastigmine/Exalon, and galantamine/Reminyl
- Conclusion
 - Flawed methods
 - Small clinical benefits—not associated with any delay in onset of AD
 - Significant side effects
 - Scientific basis for recommendations of cholinesterase inhibitors for the treatment of Alzheimer's Disease is questionable— not evidenced based.

Cholinesterase Inhibitors

- Can we prevent AD and severe dementia by using cholinesterase inhibitors in mild cognitive impairment (MCI)? Probably not.
- The use of cholinesterase inhibitors in MCI was not associated with any delay in the onset of AD or dementia.
- The side effects are significant.
- The uncertainty regarding MCI as a clinical entity raised the question as to the scientific validity of these trials.
- Raschetti, R., E. Albanese, et al. (2007). "Cholinesterase inhibitors in mild cognitive impairment: a systematic review of randomised trials." PLoS Med **4(11): e338**.



Importance of Prevention

- Current treatment options for Alzheimer's disease only address symptoms, and no treatments are available that focus on delaying the actual disease process.
- Meanwhile, an urgent need exists to find a means of preventing, delaying the onset, or reversing the course of AD.
- Since the disease typically strikes very late in life, for some people delaying its symptoms could be just as good as a cure.
- It is now widely accepted that delaying the onset of AD by just five years can cut its incidence in half (<http://www.alz.org/national/documents>)



Prevention of AD and “Type 3 Diabetes”

- The epidemic of insulin resistance/pre-diabetes and type 2 diabetes may be associated with the emergence of higher rates of Alzheimer’s disease.
- New evidence demonstrates that impaired insulin signaling may contribute to the formation of AD.
- Understanding the links between diet, insulin resistance and AD allows us to plan for early intervention.
- The risk of Alzheimer disease is probably not determined in any single time period but results from the complex interplay between genetic and environmental exposures throughout the life course.

What are the Risk Factors?

- **The risk factors for Alzheimer's disease can be classified as genetic and non-genetic.**
- **Non-genetic:**
 - **Education**
 - **People with fewer years of education appear to be at higher risk for Alzheimer's and other dementias than those with more years of education.**



Non-genetic Risk Factors

- **Disease associations**
 - **High blood pressure**
 - **Heart disease**
 - **Diabetes and insulin resistance**
 - **Having Type 2 Diabetes is associated with a 2-4 fold risk**
 - **Stroke**
 - **People with more than one of the four diseases are at even greater risk of developing Alzheimer's and other dementias.**

Non-genetic Risk Factors

- **Physical: Elevated Body Mass Index (BMI) and body fat**
 - In one study, the incidence of AD increased in men who gained weight between the ages of 30 and 45 and in women with a BMI >30 at ages 30, 40, and 45.
 - Risk of Alzheimer's comparing group with highest 20% to group with lowest 20% of body fat showed increased risk of 293%
 - So one's weight in middle-age makes a difference with AD risk later in life.
 - Overweight and obesity are associated with insulin resistance and Type 2 Diabetes.

What are the risk factors?

- **Dietary Patterns**

- **Increase risk**

- In one study, the strongest dietary risk factor for Alzheimer's disease is higher caloric and saturated and trans fat intake.
 - Higher caloric and fat intake are related to increased adiposity (fat mass), hyper-insulinemia, and diabetes.

- **Decrease risk**

- Caloric restriction
 - Dietary intake of fish and the omega-3 fatty acids (especially DHA)
 - High intake of unsaturated, un-hydrogenated fats (nuts, seeds, vegetable oils)
 - Antioxidant and anti-inflammatory foods, spices, and supplements



Calorie Restriction

- Assessment of memory function in 50 healthy to overweight subjects
- Memory assessment at onset and after 3 months.
- Caloric reduction of 30% in one group
- Significant increase of verbal memory of 20% ($p < 0.001$) in calorie restricted group
- Correlated with decreases in fasting plasma levels of insulin and high sensitive C-reactive protein, most pronounced in subjects with best adherence to the diets.
- Witte, A. V., M. Fobker, et al. (2009). "Caloric restriction improves memory in elderly humans." Proc Natl Acad Sci U S A 106(4): 1255-60.



Fish Intake, DHA & Lowered AD Risk

- Fish consumption correlated with lower AD risk
 - Fish is major source of DHA (Docosahexaenoic acid), an omega-3 fatty acid
- Low DHA levels in brains of AD patients
- Framingham Study: People in the top 25% of DHA measures in “plasma phosphatidyl choline”* showed a 47% reduced risk of dementia of all causes after 9 years
 - *phosphatidylcholine is an important component in nerve cells
- Fish 3 times weekly or more, but isn't the whole story
- Schaefer, E. J., V. Bongard, et al. (2006). "Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study." Arch Neurol 63(11): 1545-50.



DHA from Fish

- May suppress the following:
 - Activation of the tau-protein, a component of the neurofibrillary tangle.
 - Insulin resistance
 - Inflammation of nerve cells
 - Oxidative damage to nerve cells
- Increases
 - Brain derived neurotrophic factor (BDNF)
- Clinical trials do not show a clear benefit, but high DHA intakes from dietary sources may be useful as part of an overall diet, supplement, and exercise strategy.



Oxidative Stress & AD

- Your body constantly reacts with oxygen as you breathe and your cells produce energy. As a consequence of this activity, highly reactive molecules are produced known as free radicals.
- Free radicals interact with other molecules within cells. This can cause oxidative damage to proteins, membranes and genes.
- Oxidative damage has been implicated in the cause of many diseases such as cancer and Alzheimer's and has an impact on the body's aging process.
- Studies establish oxidative damage as an early event in the formation of Alzheimer disease.
 - Markesbery, W. R. and M. A. Lovell (2007). "Damage to lipids, proteins, DNA, and RNA in mild cognitive impairment." Arch Neurol **64(7): 954-6.**



Which are Dietary Antioxidants?

- Spices: tumeric (curcumin), cloves, cinnamon, ginger (spices used in curries); oregano, rosemary,
- Green tea
- Brightly colored fruits: cranberries, blueberries, and blackberries were ranked highest among the fruits studied.
- Brightly colored vegetables, as well as beans, artichokes, and Russet potatoes
- Nuts, including pecans, walnuts, and hazelnuts.



Reduced Risk of Alzheimer's Disease in Users of Antioxidant Vitamins

- Vitamin C & E
 - Use of vitamin E and vitamin C supplements in combination is associated with reduced prevalence and incidence of AD. Antioxidant supplements merit further study as agents for the primary prevention of AD. Zandi, et al. Archives of Neurology. 61. 82-88. 2004.
- Vitamin D
 - May have an antioxidant and anti-inflammatory effect, and is important to nerve cell function.



What are the Risk Factors?

- (Lack of)Exercise
 - Several studies have found that increased physical activity is inversely related to Alzheimer's disease.
 - High physical activity is typically accompanied by low adiposity, lower hyperinsulinemia, and lower diabetes risk which may be the explanation for the beneficial effects.
 - People who exercise have more blood vessels and increased blood flow to the brain.

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INSIDE 10/2/08

MS: Criteria for predicting progression in children ... **11**

TBI: New postmortem evidence of CTE in football player **12**



DEMENTIA: Abeta levels in plasma predict risk for Alzheimer disease **22**

EPILEPSY: Dopamine

Exercise Improved Mental Function in Adults At Risk for Dementia

BY DAWN FALLIK

For years, doctors have recommended exercise to lose weight, improve mood, and increase cardiac health. But now, a clinical trial in Australia has shown that exercise — even as little as 30 minutes a day — can improve mental function in adults at risk of dementia.

The study was published in the Sept. 3 *Journal of the American Medical Association*.

STUDY PROTOCOLS, FINDINGS

Investigators, led by Nicola T. Lautenschlager, MD, and col-



FDA APPROVES IMMUNE GLOBULIN PRODUCT FOR CIDP

BY ELIZABETH STUMP

In September, the FDA approved 10 percent caprylate-chromatography purified immune globulin intravenous (IGIV-C), marketed as Gamunex, for treatment of chronic inflammatory demyelinating polyneuropathy (CIDP). This is the first IVIG therapy approved to treat any neurological disease in the US, experts said.

Manufactured by Talecris Biotherapeutics, the agent was designated an orphan drug by the FDA because CIDP affects fewer than 200,000 people in the US. CIDP, an autoimmune disorder resulting in progressive generalized limb weakness, areflexia, and large fiber sensory loss, affects two to seven individuals per 100,000 worldwide.

The results of the multicenter, multinational placebo-controlled clinical trial that secured FDA approval were published in the February *Lancet*



Exercise and Memory

- JAMA: Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer's Disease: A Randomized Trial.
- 138 participants.
- Complained of mild memory dysfunction
- Intervention: 24 weeks of exercise, average 142 minutes more each week.
- Assessment of ADAS-cog scale over 18 months
- Summary: A physical activity program of an average of an additional 142 minutes of exercise per week modestly improved cognition relative to controls in older adults with subjective and objective memory impairment.



Physical Activity, Including Walking, and Cognitive Function in Older Women

- Nurses Health Study.
 - 18,766 women aged 70-81 years.
 - Cognitive testing twice over 2 years (1995-2001)
- Higher levels of long term regular physical activity were strongly associated with higher levels of cognitive function, and less cognitive decline.
- Specifically, the apparent cognitive benefits of greater physical activity were similar in extent to being about 3 years younger in age, and
- was associated with a 20% lower risk of cognitive impairment.
 - Weuve, et al. JAMA 292. September 2004. 1454-61

What are the Risk Factors?

- Genetic
 - Early –onset
 - Three genes have been identified in familial early onset Alzheimer's disease, Amyloid Precursor Protein (APP), Presenilin 1, and Presenilin 2.
 - These genes affect less than 5% of cases of Alzheimer's disease, have full penetrance and expressivity, and usually affect persons in middle age.
 - Late-onset
 - the APOE- ϵ_4 allele.
 - Importantly, APOE ϵ_4 has been found to modulate the effect of other risk factors, such as diabetes and hyperinsulinemia.

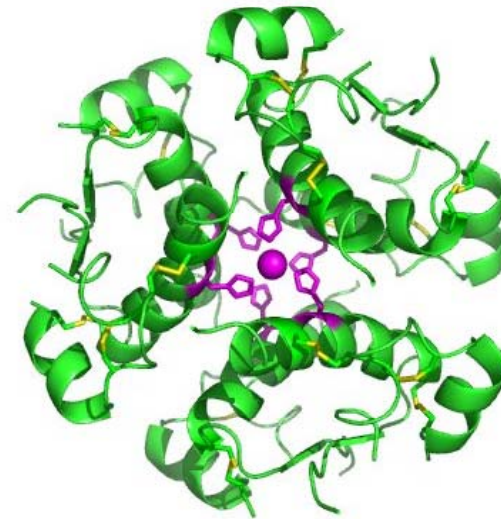
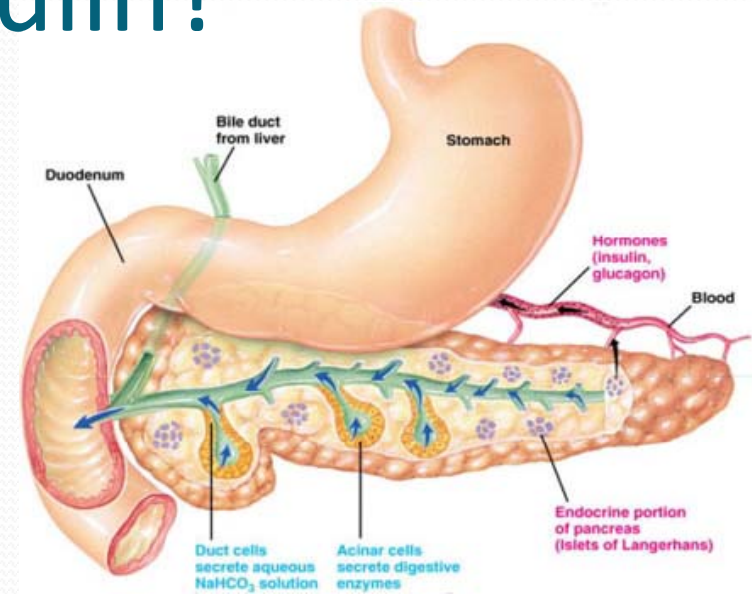


Alzheimer's as Type 3 Diabetes

- The term type 3 diabetes was coined in 2005 by Suzanne de la Monte, MD, MPH, Associate Professor of Pathology and Medicine and neuropathologist at Brown Medical School.
- Her team, examining postmortem brain tissue of AD patients, found that AD may be a disease associated with insulin signaling.
- The team termed it type 3 diabetes because it harbors elements of both types 1 and 2 diabetes, since there is both a decrease in the production of insulin and resistance to insulin receptors.

What is insulin?

- Insulin is a hormone produced in the pancreas that is central to regulating the energy and glucose metabolism in the body.
- Insulin causes cells in the liver, muscle and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscle.
- It crosses the “barrier” into the brain and is involved in delivering glucose to brain cells.
- Insulin in the brain is necessary for learning and memory.





What is “insulin resistance”?

- Insulin resistance is a condition in which the body produces insulin but does not use it properly—the cells essentially don't open the door when insulin comes knocking.
- As a result, the body needs more insulin to help glucose enter cells.
- The pancreas tries to keep up with this increased demand for insulin by producing more.
- Over time, this results in a condition called "hyperinsulinemia" or "too much insulin in the blood."
- Additionally “insulin resistance” affects over 200 other metabolic pathways.



Insulin and the Brain

- The human brain uses glucose as a primary fuel.
- Insulin secreted by the pancreas cross the blood-brain barrier (BBB), reaching neurons and glial cells, and exerts a region-specific effect on glucose metabolism.
- Glucose homeostasis is critical for energy generation, the creation and survival of neurons, neurotransmitter regulation, and synaptic plasticity.
- Glucose also plays a key role in cognitive function.
- Think of insulin as water in the Rhyme of the Ancient Mariner:
 - **Water, water, everywhere,**
 - **And all the boards did shrink;**
 - **Water, water, everywhere,**
 - **Nor any drop to drink.**

How does insulin resistance contribute to AD?

- Chronic “peripheral” (outside of the central nervous system/brain) hyperinsulinemia leads to:
 - Reduced insulin transport across the blood brain barrier and a reduced insulin signaling in brain, altering all of insulin's actions
 - Increased amyloid β secretion and decreased removal (amyloid β forms the AD “plaques”)
 - Increased tau “hyperphosphorylation” (which forms the AD “tangles”)
 - Increased development of “ADDLs”
 - Small molecules that are more harmful than amyloid to the brain.
 - ADDLs prevent insulin from working in the brain, thus interfering with memory formation
 - Multiple changes that trigger degeneration of brain cells and a decline in cognitive function.



How does insulin resistance contribute to AD?

- Insulin is also needed to stimulate acetylcholine, which is a neurotransmitter, production.
 - Acetylcholine is needed for memory.
 - Current treatments for AD symptoms slow the breakdown of acetylcholine.
- High peripheral insulin levels also increase inflammation in the brain, which also contributes to AD.



Type 3 Diabetes and AD

- AD is characterized by both **low insulin levels and insulin resistance within the brain**, as opposed to type 2 diabetes, which is characterized by high insulin levels and insulin resistance outside of the central nervous system or brain.
 - **80% decrease in number of insulin receptors in the brain**
 - **Ability of insulin's ability to bind to receptor is also compromised**



The search for insulin-related treatment of AD

- Early research has shown treatment with nasal insulin to be associated with minor memory improvement
 - Nasal insulin raises brain insulin without raising plasma insulin levels.
 - May not work in people with ApoE4 genetic predisposition.
- Early small studies of Avandia (rosiglitazone) improved cognitive function in some AD patients, but a larger study showed no effect.
 - In February 2010, David Graham, the FDA's associate director of drug safety, recommended that rosiglitazone be taken off the market. Graham argued that rosiglitazone caused 500 more heart attacks and 300 more heart failures than its main competitor.



The search for insulin-related treatment of AD

- Finally, people with Type 2 diabetes who maintain less than optimal glycemic control (i.e. with many occurrences of high blood glucose levels) are more likely to start manifesting cognitive deficits.
- Interestingly, improving glycemic control in this population can reduce these cognitive deficits, suggesting that cognitive deficits might not be permanent in patients in whom presentation is early.



Causes of Insulin Resistance: Dietary Factors 1

- “High calorie intake and diets high in sugar and refined flour are major health concerns in the Western diet; along with sedentary lifestyles, they have been linked to an increased relative risk of AD.”
- **Glucose “overload”**
 - “These data underscore the potential role of dietary sugar in the pathogenesis of AD and suggest that controlling the consumption of sugar-sweetened beverages may be an effective way to curtail the risk of developing AD.”-- J Biol Chem 282, 50: 36275-82, 2007.
- **Fiber “shortage”**
 - Refined grains in breads, pasta, crackers, etc.
 - Fewer legumes & legumes bred for less fiber (soluble fiber)
 - Fewer high fiber fruits and vegetables



Causes of Insulin Resistance: Dietary Factors 2

- Calorie and fat “overload”
 - Marbled meat from inactive/immobilized feedlot animals
 - “Partially hydrogenated” vegetable oils or “trans” fats
 - Eating out: gourmet, family, and fast-food restaurants
 - Large portion sizes



Causes of Insulin Resistance: Dietary Factors 3

- Insufficient vitamins, minerals, and micronutrients from eating too few whole grains, fruits and vegetables, and insufficient sunlight.
- Insufficient phytonutrients (fruits and vegetables)
- Additives that interfere with cell signaling mechanisms and structures.



Good fats/Bad fats

- **Good fats: Omega 3's**
 - Alpha-linolenic acid (found in fish, canola, flax, hemp seed, soy bean, and walnut oil and dark green leaves)
 - docosahexanoic acid (DHA) and eicosapentanoic acid (EPA), largely found in fish
 - olive oil
- **Bad fats**
 - Trans fats (partially hydrogenated vegetable oil)
 - Saturated animal fat (milk fat, beef tallow, lard, etc.)



Dietary Recommendations

- “Pending further study, it is prudent to recommend to those at risk for AD – e.g. with a family history or features of metabolic syndrome, such as obesity, insulin insensitivity, etc. – to avoid foods and beverages with added sugars; to eat whole, unrefined foods with natural fats, especially fish, nuts and seeds, olives and olive oil; and to minimize foods that disrupt insulin and blood sugar balance.”
 - J. Neurochem. (2008) 106, 1503–1514



Practical Dietary Guidelines

- **Avoid foods with added sugars.**
- **Increase consumption of fruits, vegetables, and legumes.**
- **Consume fruits that are less-ripe instead of overripe (i.e., bananas).**
- **Consume grain products processed according to traditional rather than modern methods (e.g., *al dente* pasta, stone-ground breads, old-fashioned oatmeal)**
- **Avoid puffed grains and finely ground flour/grain products**
- **Acid in food lowers GI (i.e., sourdough bread has a lower GI than non-sourdough bread).**
- **Limit intake of potatoes and concentrated sugars.**
- **In general, reduce consumption of “white foods” (white potatoes, white breads, white pasta) and increase consumption of multicolored, whole, non-processed foods.**
- **The following website is a good resource for information on the glycemic index: www.glycemicindex.com/**

ApoE4: Genetic-environment considerations

- A genetic factor in late-onset Alzheimer's disease (Alzheimer's disease developing at age 65 or older) is apolipoprotein E-e4 (ApoE-e4).
- ApoE-e4 is one of three common forms of the ApoE gene, which provides the blueprint for a protein that carries cholesterol in the bloodstream.
- Everyone inherits one form of the ApoE gene from each of his or her parents.
- Those who inherit one ApoE-e4 gene have a greater risk of AD
 - 2.2 greater for Hispanic Americans
 - 3.2 times greater risk for non-Hispanic whites.
- Those who inherit two ApoE-e4 genes have an even higher risk.
 - 14.9 times higher for whites
 - 5.7 times higher for African-Americans

ApoE4: Genetic-environment considerations

- ApoE4 allele-positive individuals account for 40-50 percent of sporadic late-onset AD.
- APOE ϵ_4 is associated with higher cholesterol and “hardening of the arteries,” which is a factor in AD.
- Fortunately, dietary changes are successful in lowering cholesterol in people with APOE ϵ_4 .





APOE ϵ 4 and Diabetes: Double the Trouble

- One recent study suggest that in people that have both diabetes and an ApoE4 allele, the risk of developing Alzheimer's disease is more than double the risk of people with an ApoE4 allele without diabetes.
- Diabetes dramatically increases the amyloid deposition and neurofibrillary tangles in people with the ApoE4 genotype.
- In people with other risk factors such as ApoE4 allele, diabetes appears to lead to a more dramatic increase in Alzheimer's disease pathology.

Summary goals for reducing risk factors

- **Correct metabolic abnormalities**
 - Reduce Insulin resistance
 - Reduce Inflammation & Oxidative Stress
 - Lower elevated Homocysteine
- **Reduce atherosclerosis**
 - Blood pressure control
 - Normalize blood fats (Cholesterol)
 - Promote Endothelial health (Omega 3's)
- **Maintain optimal Exercise**
- **Avoid exposure to toxins**
 - If smoking, quit
 - Organic animal products and selected produce
 - Avoid toxins in Plastics, and other environmental toxins
 - Limit alcohol use (Alcohol is not a health food)
 - Limit exposure to toxic heavy metals
 - Drink filtered water



Resources

- **Books about healthy foods.**
 - Pollan, Michael: *In Defense of Food*
 - Mark Hyman: *Ultramind , Ultrametabolism and The Ultrametabolism Cookbook.*
- **For info about pesticides in foods, water filters, hazards of plastics, etc: Environmental Working Group <http://www.ewg.org/>**