Insulin Resistance, Obesity and Brain Health
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Chronic Diseases in South Florida

Prevalence of Chronic Disease in Medicare Beneficiaries (2013 Data)

<table>
<thead>
<tr>
<th>Chronic Disease</th>
<th>National</th>
<th>Florida</th>
<th>Palm Beach County</th>
<th>Broward County</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beneficiaries</td>
<td>34,126,305</td>
<td>2,243,566</td>
<td>174,150</td>
<td>155,379</td>
</tr>
<tr>
<td>Mean Age, y</td>
<td>71</td>
<td>73</td>
<td>75</td>
<td>73</td>
</tr>
<tr>
<td>Gender, % Female</td>
<td>55.1</td>
<td>54.7</td>
<td>56.2</td>
<td>55.8</td>
</tr>
<tr>
<td>Dual-eligible, %</td>
<td>21.7</td>
<td>19.3</td>
<td>11.2</td>
<td>23.9</td>
</tr>
<tr>
<td>Alzheimer’s Disease (%)</td>
<td>9.8</td>
<td>11.3</td>
<td>11.5</td>
<td>12.7</td>
</tr>
<tr>
<td>Coronary Heart Disease (%)</td>
<td>28.5</td>
<td>37.1</td>
<td>42.7</td>
<td>37.8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>27.8</td>
<td>28.5</td>
<td>28.9</td>
<td>29.1</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>11.9</td>
<td>13.6</td>
<td>9.7</td>
<td>12.4</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>55.5</td>
<td>60.8</td>
<td>60.3</td>
<td>58.8</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>44.7</td>
<td>55.5</td>
<td>60.2</td>
<td>52.9</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>3.8</td>
<td>4.5</td>
<td>4.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Forecast of Alzheimer’s Disease Prevalence

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2030</th>
<th>2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD Prevalence Age 65+ Years</td>
<td>19%</td>
<td>42%</td>
<td>54%</td>
</tr>
<tr>
<td>5.2 Million (est)</td>
<td>7.3 Million (est)</td>
<td>16.0 Million (est)</td>
<td></td>
</tr>
</tbody>
</table>

What is Alzheimer’s Disease (AD)?

• Most common cause of dementia
• 5.4 million Americans have AD
• 250,000 age < 65 years (early-onset)

Annual treatment costs $200 billion
• Costs increase as disease progresses
• 3rd most expensive: heart, cancer
• Sixth leading cause of death (over age 70)
• Makes up 50% of all nursing home beds
• Median cost (2015) = $88,000

Florida Statistics

• 6.5% of Medicare beneficiaries
• 510,000 cases (2016)
• 720,000 cases (2025)
• Per capita cases 14%
• 5093 deaths
• Mortality: 26/100,000
• >1 Million caregivers
• 1.2 Million hours
• Care valued at $15 Million
• Medicaid: $2.3 Billion

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  • Mangurian Foundation
  • Langbert Foundation

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**Clinical Expression of AD may evolve from different etiologies**

- Can prevent or treat AD by addressing:
  - AD pathology (plaques, tangles)
  - Other pathologies and mechanisms

**Diabetes and the Risk of AD**

<table>
<thead>
<tr>
<th>Diabetes subtype</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total AD</td>
<td>1.0 (1.0 to 1.0)</td>
</tr>
<tr>
<td>Without cerebrovascular disease</td>
<td>1.0 (1.0 to 1.0)</td>
</tr>
<tr>
<td>With cerebrovascular disease</td>
<td>2.0 (1.0 to 4.0)</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>2.0 (1.0 to 4.0)</td>
</tr>
<tr>
<td>Other dementia</td>
<td>1.0 (1.0 to 1.0)</td>
</tr>
</tbody>
</table>

Subjects without diabetes served as reference. Values are relative risk (95% CI).

**Regulation of Insulin Resistance in the Brain**

- Brain insulin resistance appears to be an early and common feature of AD
- AD has been proposed as a "type 3 diabetes" representing a form of diabetes that selectively involves the brain
- Amyloid pathology as a major mediator of brain insulin resistance in AD
- Recently, tau protein has been identified as a modulator of brain insulin signaling
- Insulin resistance markers such as insulin-like growth factor (IGF-1) and insulin receptor substrate (IRS-1) are associated with poor cognitive performance
- Insulin degrading enzyme (IDE) may play a role in degrading amyloid protein in the brain

**Receptors for Advanced Glycation End-Products (RAGE)**

- RAGE and its ligands contribute to activation, polarization, and maturation of T cells and antigen-presenting cells
- AGEs are modified proteins, globulins, and nucleic acids associated with diabetes risk
- May induce changes in adaptive immunity, islet cell function, oxidative stress, and systemic inflammation
- Lead to cross-linking of intracellular and extracellular proteins

**Link Between Obesity and Alzheimer’s Disease**

- Obesity prevalence is increasing steadily throughout the world's population in most countries and in parallel the prevalence of metabolic disorders including cardiovascular diseases and type 2 diabetes is also rising
- Less is reported about excessive adiposity relationship with poorer cognitive performance, cognitive decline and dementia
- The precise mechanisms that underlie the connections between obesity and the risk of cognitive impairment are still largely unknown
  - insulin resistance
  - the gut-brain axis
  - systemic mediators and central inflammation processes
Link between Diabetes and Alzheimer’s disease

- Adiponectin is an anti-inflammatory adipokine
  - Low levels are associated with vascular disease and diabetes
  - Elevated levels are associated with neurodegenerative disease.
- Leptin is a pro-inflammatory adipokine
  - Elevated levels are associated with diabetes and vascular disease
  - Low levels are associated with neurodegenerative disease.

Adipokines and risk of Alzheimer Disease

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Obesity and risk of AD

- Cross-sectional studies demonstrate HDL and ApoE levels are inversely associated with dementia
- Higher levels of ApoE are marker of prevalent dementia not associated with future dementia
- Polyunsaturated fatty acids may be neuroprotective

Lipids and Dementia

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- Higher levels of ApoE are marker of prevalent dementia not associated with future dementia
- Polyunsaturated fatty acids may be neuroprotective

Genetic Link Between Adiposity and AD

- Genome-wide association meta-analysis of body fat percentage (BF%) in 100,716 individuals.
- Twelve loci reached genome-wide significance (P<5×10⁻⁸)
- Eight were previously associated with adiposity
- Four (in or near COBLL1/GRB14, IGF2BP1, PLA2G6, CRTC1) were novel associations
- Seven loci showed a larger effect on BF% than on BMI, suggestive of a primary association with adiposity, while five loci showed larger effects on BMI than on BF%, suggesting association with both fat and lean mass.
- In particular, the loci more strongly associated with BF% showed distinct cross-phenotype association signatures with a range of cardiometabolic traits revealing new insights in the link between adiposity and disease risk.

Nutrition and the Risk of Dementia

- Higher intake of vitamin B₁₂, vitamin D and ω-3 PUFA EPA from food sources was associated with lower Aβ load
- Higher β-carotene and folate intake was associated with higher brain glucose metabolism
- Higher consumption of saturated fats was associated with lower brain glucose metabolism
- Cross-sectional studies demonstrate HDL and ApoE levels are inversely associated with dementia
- Polyunsaturated fatty acids may be neuroprotective
**Mediterranean Diet**

- High in grains, olive oil, legumes, cereals, fish
- Low in saturated fats, red meats
- Moderate wine with meals
- Reduces risk of developing dementia
- Reduces mortality by 73% once dementia develops
- Higher MeDi scores were associated with a smaller hip-to-waist ratio ($\beta=-0.25, p=0.03$)  
  

**MIND Diet**

- Mediterranean-DASH (Dietary Approaches to Stop Hypertension) Intervention for Neurodegenerative Delay Diet
- Combine two dietary plans
- Mediterranean: whole plant foods, grains, legumes, vegetables, fruit, nuts, fish, modest alcohol (red wine)
- DASH: fruit, vegetables, low-fat dairy produces, whole grains, poultry, fish, nuts

**Brain Healthy**
- Green leafy vegetables
- Other vegetables
- Nuts
- Berries
- Beans
- Whole grains
- Fish
- Poultry
- Olive oil
- Wine

**Unhealthy**
- Red meats
- Butter and stick margarine
- Cheese
- Pastries and sweets
- Fried or fast foods

**MIND Diet**

- MeDi scores were significantly associated with volumes of orbitofrontal cortex, entorhinal cortex and posterior cingulate cortex

**Multicultural Community Dementia Screening**

- Supported by 2 grants from the National Institute on Aging
- Combine two dietary plans
- Mediterranean: whole plant foods, grains, legumes, vegetables, fruit, nuts, fish, modest alcohol (red wine)
- DASH: fruit, vegetables, low-fat dairy produces, whole grains, poultry, fish, nuts

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**MIND Diet**

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**Measurement Tools**

- Sphygmomanometer: Blood pressure
- Dynamometer: Grip Strength
- Body Composition Impedance
- Handgrip (estimated)
- Water
- Lean Muscle
- Fat
- Body Visceral

**Multicultural Community Dementia Screening**

- Supported by 2 grants from the National Institute on Aging
- Community-based assessment of older adults (target goal 500)
- Demographics, financial resources, preferences
- Cognitive Behavioral Screening (memory, mood)
- Physical assessment (balance, gait, strength)
- Anthropometric measurements
- Social work follow-up
- Subset have Gold Standard testing and biomarkers collected
- MRI scans
- PET scans
- EEG
- Blood and spinal fluid
- Repository of multicultural medical, cognitive, and imaging biomarker data: 500 individuals with grant protocol (187,500 data points); a subset of 150 individuals with a Gold Standard evaluation (202,500 data points), structural and functional MRI, FDG-PET (SUVR), and high density EEG (125,000 data points) + raw and processed images.
Elevated Hemoglobin A1C and Cognitive Impairment

- Hemoglobin A1C relates to average plasma glucose concentration over previous 2-3 months
- Higher amounts of A1C indicates diabetes risk, poorer control of blood glucose, and risk of heart, kidney and retinal disease
  - For diabetics, goal is below 6%
  - Categories
    - Normal (reference): <5.6%
    - Pre-diabetes: 5.7‐6.4%
    - Diabetes: >6.5%

Blood Based Biomarkers

<table>
<thead>
<tr>
<th>Lipid Profile</th>
<th>Renal Function</th>
<th>Genetic Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>Creatinine</td>
<td>MTHFR C677T</td>
</tr>
<tr>
<td>LDL-C-direct</td>
<td>Est Glomerular Filtration Rate</td>
<td>MTHFR A1298C</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>HOMA-IR</td>
<td>Endocrine</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Electrolytes</td>
<td>TSH</td>
</tr>
<tr>
<td>LDL-p by NMR</td>
<td>Glucose</td>
<td>T4 Total</td>
</tr>
<tr>
<td>Small LDL-p by NMR</td>
<td>Hemoglobin A1C</td>
<td>T3 Total</td>
</tr>
<tr>
<td>HDL-p by NMR</td>
<td>Est Average Glucose</td>
<td>Testosterone Total</td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td>25-hydroxy-vitamin D</td>
<td>Sex Hormone Binding Protein</td>
</tr>
<tr>
<td>Hs-CRP</td>
<td>Vitamin B12</td>
<td>Omega-3 index</td>
</tr>
<tr>
<td>Myeloperoxidase</td>
<td>Methyhamelinic acid</td>
<td>Neurodegeneration</td>
</tr>
</tbody>
</table>
| Heart Type Fatty Acid Binding Protein | RBC Folate | -
| Cortisol | - | -
| Adiponectin | - | -
| Leptin | - | -

Renal Function
- Est Glomerular Filtration Rate
- Creatinine
- Electrolytes
- Glucose
- Hemoglobin A1C
- Est Average Glucose
- 25-hydroxy-vitamin D
- Homocysteine
- Vitamin B12
- Methyhamelinic acid
- RBC Folate
- Omega-3 index

Genetic Markers
- MTHFR C677T
- MTHFR A1298C
- Factor V Leiden
- Prothrombin

Endocrine
- TSH
- T4 Total + Free
- T3 Total
- Testosterone Total + Free
- Sex Hormone Binding Protein
Links between Diabetes and Alzheimer’s Disease

- B-Amyloid
- Insulin signaling
- Insulin degrading enzyme
- Inflammation
- Oxidative stress
- Mitochondrial dysfunction
- Advanced glycation end products
- ApoE4
- Cholesterol

Clinical Expression of AD Revisited

- APOE leads to clinical AD through AD pathology
- Diabetes may lead to clinical AD through infarctions
- Obesity may lead to clinical AD through inflammation

Study of Nasal Insulin in the Fight Against Forgetfulness (SNIFF) Trial

- Novel therapeutic approach using intranasal insulin (INI) has shown promise in short-term clinical trials
- Provide evidence for the mechanisms through which INI may produce benefits by examining key cerebral spinal fluid (CSF) biomarkers and hippocampal/entorhinal atrophy
- 240 people with aMCI or AD will be given either INI or placebo for 12 months, following an open-label period of 6 months

TOMMorow Study

- 3500 individuals age 65-83 with normal thinking and memory were enrolled
- Have polymorphism of TOMM40 gene (possibly increased risk of AD)
- Five years of treatment with pioglitazone, an anti-diabetes drug

Summary

- Multiple medical conditions increase the risk of neurodegeneration
- May also be multiple pathways to diagnose, treat, cure or prevent
- Detection of and interventions addressing root causes (diabetes, obesity) may offer novel approaches to diagnosing, treating, curing, or preventing Alzheimer’s disease
- A number of exciting pharmaceutical approaches are attempting to modify AD pathology
- Many are now targeting pathways related to diabetes
- Modifiable risk factors (lifestyle, exposure, environment, co-morbid disease) are excellent targets to personalize approach to medical care
- AD and PD are diseases of a lifetime; may be many ways to build a better brain as we age
- At FAU, we are spearheading game-changing approaches to improve the lives of our patients and their families

“An Ounce of Prevention is Worth a Pound of Cure” - Benjamin Franklin