Women, Menopause, Insulin Resistance and Alzheimer’s: What is the link?

Filomena Trindade, MD, MPH, ABFM, ABOIM
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Presenter
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Women, Menopause, Insulin Resistance and Alzheimer’s: What is the link?

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Objectives for This Presentation

• Gain a basic understanding on the pathophysiology of mild cognitive decline and Alzheimer’s and how it relates to insulin resistance and the menopausal transition in women
• Review the potential mechanisms of diabetes type 2 and how it contributes to Alzheimer’s disease in women
• Identify the hallmarks of hormone replacement with respect to Alzheimer’s disease in women
Incidence of Alzheimer’s by Sex

Incidence Per 1,000 Person Years

Age

Gender
- Female
- Male
“The color scale reflects brain activity, with brighter colors indicating more activity, and darker colors indicating lower activity. The scan to the right (menopause) looks 'greener' and overall darker, which means that the woman's brain has substantially lower brain activity (more than 30 percent less) than the one to the left (no signs of menopause).”
This study demonstrated that, in early midlife, women outperformed age-matched men across all memory measures, but sex differences were attenuated for postmenopausal women.

Initial learning and memory retrieval were particularly vulnerable, whereas memory consolidation and storage were preserved.

Findings underscore the significance of the decline in ovarian estradiol production in midlife and its role in shaping memory function.
The onset of menopause in mid-life elevates the vulnerability of women to AD, an increased risk that is likely associated with the depletion of estrogens. Menopause is also linked with an abundance of additional changes, including increased central adiposity and inflammation.
“Alzheimer’s disease (AD) is a multifactorial disorder in which multiple risk factors are theorized to interact in regulating pathogenesis. As depicted in the diagram an essential factor in AD is increasing age, which is also associated with elevated inflammation and, in women, menopause. The loss of estrogens at menopause increases central adiposity, which in turn increases inflammation and predisposes women to metabolic syndrome, insulin resistance, and AD. Individually and cooperatively, aging, menopause, adiposity, and inflammation lead to cognitive deficits and AD.”

Brain insulin resistance thus appears to be an early and common feature of AD, a phenomenon accompanied by IGF-1 resistance and closely associated with IRS-1 dysfunction.
“Type 2 DM might be a risk factor for MCI progressing into AD.”
"We conclude that the term type 3 diabetes accurately reflects the fact that AD represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlap with both type1DM and T2DM."
"Type 3 DM is a neuroendocrine disorder that represents the progression of type 2 DM to AD."
Mechanism through which insulin and amyloid beta are linked.
Figure 3. Interaction of selected proteins from the network supposedly followed in T3D (mutated proteins are highlighted in red). Final protein-interaction network was framed which includes mutated and differentially expressed proteins which link Type 2 Diabetes and Alzheimer’s disease.
Figure 4. Hallmarks of Type 3 Diabetes. Attributes of Type 3 Diabetes represents the disturbed metabolic processes and pathways in Type 3 diabetes.
“Existing evidence does not support an association between indices of prolonged exposure to female hormones and lower dementia risk. There are indications, however, for better cognitive performance and delayed cognitive decline, supporting a link between female hormone deficiency and cognitive aging.”
“Findings of 9 randomized clinical trials of estrogen containing hormone therapy in Alzheimer’s disease suggested that hormone therapy does not improve cognitive symptoms of women with Alzheimer’s disease.”
Recent studies, such as WHIMS-Young, the Kronos Early Estrogen Prevention Study and the Early versus Late Intervention Trial with Estradiol targeted the younger women, and indeed showed that hormone therapy may have positive cognitive outcomes in this age group.
“Sex hormones, particularly estrogens possess potent antioxidant properties and play important roles in maintaining normal reproductive and non-reproductive functions. They exert neuroprotective actions and their loss during aging and natural or surgical menopause is associated with mitochondrial dysfunction, neuroinflammation, synaptic decline, cognitive impairment and increased risk of age-related disorders. Moreover, loss of sex hormones has been suggested to promote an accelerated aging phenotype eventually leading to the development of brain hypometabolism, a feature often observed in menopausal women and prodromal Alzheimer’s disease (AD).”
“This review points to possible reasons for these mixed data by considering the issues of both preclinical and clinical trials, in particular, the representativeness of animal models, timing of HT initiation, type of HT (different types of estrogen compounds, estrogen monotherapy vs. estrogen-progesterone combined therapy), mode of drug delivery (subcutaneous, transdermal, oral, or intramuscular), and hormone dosage used, as well as the heterogeneity of the postmenopausal population in clinical trials (particularly considering their sAD stage, anti-AD therapy, and hysterectomy status).”
“Recent advances in menopause hormone therapy including transdermal estrogen therapy have favorably influenced the balance of benefits and risks. A case can be made for menopause hormone therapy in healthy postmenopausal women for 5–10 years starting during the menopausal transition (the ‘window of opportunity’), together with all other protective measures, to delay or prevent the development of ARCID in later life.”
Given all this, how do you approach the menopausal woman?
...the optimal window of opportunity for therapeutic intervention in women is early in the endocrine aging process.
No Two Women Are The Same
If no two women are the same, how do we as clinicians personalize our approach?
“Detecting at risk individuals within a healthy population is critical for preventing or delaying Alzheimer’s disease. Systems biology integration of brain and body metabolism enables peripheral metabolic biomarkers to serve as reporters of brain bioenergetic status.”
The Saudade Hormonal Symphony™

- Insulin
- Adrenal
- Estrogen Metabolism
- Sex Hormones
- Thyroid

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Disruptors of Hormonal Function

- Traumatic emotional events
- Physical trauma
- Chronic sleep deprivation
- Infections
- Aging
- Inflammatory diseases
- Single nucleotide polymorphisms (SNPs)

- Exogenous toxins
- Acute physical stress
- Nutritional insufficiencies
- Food allergy, intolerance, or sensitivity
- Changes in gut microbiota
- Altered biotransformation
- Pharmaceuticals

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"Listen to your patient, (s)he is telling you the diagnosis."
-Sir William Osler
That Story Is Typically Told As...

- Chief Complaint (CC)
- History of Present Illness (HPI)
- Past Medical History (PMH)
- Surgical History
- Family History (FH)
- Dietary History
- Supplement and Medication History
- Lifestyle, Social, and Exercise History
- Physical Exam Findings
- Laboratory Evaluation
The Saudade Hormonal Symphony™

- Insulin
- Adrenal
- Estrogen Metabolism
- Sex Hormones
- Thyroid
Insulin’s Effects

• Effects CBO, lipid, metabolism

• Insulin effects thyroid function... and thyroid function effects insulin production

• Insulin effects endothelial function

• Other hormones...

Menopausal Complaints Are Associated With Cardiovascular Risk Factors

Gerrit-Cor M. Gast, Diederick E. Grobbee, Victor J.M. Pop, Jules J. Keyzer, Colette J.M. Wijnands-van Gent, Göran N. Samtsev, Peter M. Nilsen, Yvonne T. van der Schouw

Abstract—It has been hypothesized that women with vasomotor symptoms differ from those without with respect to cardiovascular risk factors or responses to exogenous hormone therapy. We studied whether the presence and extent of menopausal complaints are associated with cardiovascular risk profile. Data were used from a population-based sample of 5523 women, aged 46 to 57 years, enrolled between 1994 and 1995. Data on menopausal complaints and potential confounders were collected by questionnaires. Total cholesterol, systolic and diastolic blood pressures, and body mass index were measured. Linear and logistic regression analyses were used to analyze the data. Night sweats were reported by 38% and flushing by 39% of women. After multivariate adjustment, women with complaints of flushing had a 1.22 mmol/l (95% CI: 0.15 to 0.36) higher cholesterol level, a 0.60 kg/m² (95% CI: 0.18 to 0.89) higher body mass index, a 1.59 mm Hg (95% CI: 0.52 to 2.67) higher systolic blood pressure, and a 1.59 mm Hg (95% CI: 0.09 to 1.09) higher diastolic blood pressure compared with asymptomatic women. Flushing was also associated with hypercholesterolemia (odds ratio: 1.92; 95% CI: 1.52 to 2.41) and hypertension (OR: 1.20; 95% CI: 1.07 to 1.34). Results were similar for complaints of night sweating. The findings support the view that menopausal complaints are associated with a less favorable cardiovascular risk profile. These findings substantiate the view that differences in the presence of menopausal symptoms as a reason for using hormone therapy could explain discrepant findings between observational research and trials. (Hypertension. 2008;51(6):1492-1498.)

Key Words: menopausal complaint § cholesterol § blood pressure § cardiovascular risk profile § women

A number of observational studies demonstrated a protective association between hormone therapy (HT) and cardiovascular disease (CVD).1,2 Placebo-controlled, randomized trials, however, could not confirm a cardioprotective effect and showed no overall benefit of HT on the risk of cardiovascular events.3

Many potential reasons have been proposed to explain this apparent discrepancy between the observational studies and the trials. An important difference is that, in the observational studies, the most common reason to initiate HT was to relieve menopausal complaints. In contrast, in the trials, women with severe complaints were either excluded or composed only a minority of the total randomized population. Results of a recent subgroup analysis of the combined Women’s Health Initiative trials showed that women who initiated HT close to menopause had a reduced coronary heart disease (CHD) risk compared with the increase in CHD risk among women initiating HT more distant from menopause. Moreover, among women 50 to 59 years of age at enrollment in the Women’s Health Initiative, end-of-trial coronary calcium scores were lower in women assigned to estrogen plus in those assigned to placebo.

We hypothesized that complaints may alter cardiovascular risk factors. Indeed, women with a higher level of plasma estrogen level and postmenopausal women had higher vascular reactivity in studies demonstrated the increased blood pressure analysis of the combination showed that the highest from menopause appears a subset of women who may be at higher risk. We examined whether the presence of menopausal complaints is correlated with CVD risk profile in a large, community-based sample of perimenopausal women.

“The findings support the view that menopausal complaints are associated with a less favorable cardiovascular risk profile.”
Hot flashes were associated with a higher HOMA index, an estimate of insulin resistance, and to a lesser extent higher glucose. Metabolic factors may be relevant to understanding the link between hot flashes and cardiovascular disease risk.
In summary, VMS were associated with insulin resistance, as measured by the HOMA index, over a period of approximately 8 yr. These findings may contribute to ongoing efforts to better understand any mechanisms linking hot flashes to cardiovascular health.
“Our results suggest that VMS in postmenopausal women are associated with increased insulin resistance.”
Dietary Management for the Patient with Insulin Resistance

• Decrease insulin stimulation
  – Dietary modifications which decrease insulin release:
    • Fiber, 10-12 servings of vegetables and low glycemic load fruits
    • ‘Good’ (vs. ‘bad’) fat
    • ‘Good’ (vs. ‘bad’) carbohydrates
    • Protein at every meal
    • Elimination of most inflammatory food: Wheat, dairy, soy, corn, nightshades....

• Modify Gut Microbiota
  – Food first, high fiber
  – Fermented foods
  – Probiotics/prebiotics
Dietary Management for the Patient with Insulin Resistance

• Increase cellular responsiveness to insulin
  – Agents that modify insulin responsiveness at the cellular level:
    • Spices
    • Herbs
    • Chromium
    • Vitamin D
    • Magnesium
    • Omega-3
“We finally discussed AD as the potential type 3 diabetes, and the potential of restoring brain insulin levels or glucose energy metabolism via administration of intranasal insulin and use of ketogenic diets.”
The Saudade Hormonal Symphony™
Cortisol and DHEA Derive from Same Precursors
Progesterone → Pregnenolone → Cholesterol

Stress

Progestrone → Aldosterone → Cortisol → Cortisone

DHEA → DHT → Estrone (E1) → Estradiol (E2)
The Big Picture: Selye’s General Adaptation Syndrome

• **Stage 1: Arousal**
  – Both cortisol and DHEA increase with episodic stress, but recovery occurs to baseline
  – This may be asymptomatic

• **Stage 2: Adaptation**
  – Cortisol chronically elevated, but DHEA declines
  – “Stressed,” anxiety attacks, mood swings, depression

• **State 3: Exhaustion**
  – Adrenal insufficiency / low cortisol and DHEA
  – Depression and fatigued

The Saudade Hormonal Symphony™

- Insulin
- Adrenal
- Estrogen Metabolism
- Sex Hormones
- Thyroid
Thyroid Function

Hypothalamus → TRH → Pituitary → TSH → Thyroid Gland

Liver or Kidney: 95% T4

(5 deiodinase) → rT3 (Inactive)
(5’d deiodinase) (Se) → T3 (Active)

~85% → Cell Nucleus

5% T3
Stress and Thyroid Function

Hypothalamus → TRH → Pituitary → TSH → Thyroid Gland

Liver or Kidney → 95% T4 → Cell Nucleus

rT3 (Inactive) → STRESS → T3 (Active) → STRESS

5% T3
The Saudade Hormonal Symphony™

- Insulin
- Adrenal
- Thyroid
- Sex Hormones
- Estrogen Metabolism
Perimenopause

Months

FSH
Estrogen
Progesterone
Breast Cancer Risks and HRT

• Follow-up on the French E3N cohort study
  – 80,377 postmenopausal women found “when combined with an estrogen, progesterone has a safer risk profile in the breast compared with some other progestogens.”
“Co-administration of CEE with MPA or MP caused differential effects on memory in postmenopausal women.”
“Compared with healthy women, poor metabolic women had significantly lower executive, global and memory cognitive performance. Hormone therapy provided metabolic benefit to women in high blood pressure and poor metabolic phenotypes.”
A. Adjusted for menopause cohort and randomized intervention

Global Cognition Composite Score

B. Adjusted for menopause cohort, randomized intervention, and education

Global Cognition Composite Score

Verbal Memory Composite Score

Executive Functions Composite Score

Will Memory be Lost with Menopause

“It is possible that timing of the start of hormone replacement therapy exactly to the menopause could provide the best benefit of memory and inflammation processing.”
“Use of 17 β-estradiol in young and healthy post-menopausal women yields the maximum benefit when the neurons are intact or neuronal stress has just started. Hence intervention in the critical period is key in the prevention or delay of AD in post-menopausal women.”
The Saudade Hormonal Symphony™
Estrogen Metabolism

- Cholesterol
  - Pregnenolone
    - Progesterone
      - Corticosterone
        - Aldosterone
  - 17-OH-Pregnenolone
    - 17-OH-Progesterone
  - Cortisol
  - Cortisone

- DHEA
  - Androstenedione
    - Testosterone
      - DHT

- Estrone (E1)
  - Estradiol (E2)
    - 2-OHE1
      - 2-MoE1
    - 16a-OHE1
      - Estriol (E3)
    - 4-OHE1
      - 4-MoE1

(Mineralocorticoids) (Glucocorticoids) (Androgens) (Estrogens)
Endocrine Disruptors

• Environmental xenobiotics act as “endocrine disruptors” that modify intercellular communication and function
• Chemicals commonly detected in people include DDT, Polychlorinated biphenyls (PCB's), Bisphenol A, Polybrominated diphenyl ethers (PBDE's)
• May play role in cancer and obesity
• Changes in DNA methylation (epigenetic modification) which can ultimately change ER activity
• A higher ratio of the 4 and 16 hydroxylated-estrogen derivatives that are potentially more genotoxic
  – Modifying members of the CYP450 enzyme family
CONNECTING THE DOTS TO FIND THE ROOT CAUSE...

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&

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The Sacred Island of Sao Jorge

Register at: http://www.drtrindade.com/saudadetotalwellnessretreat

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Questions?

Filomena Trindade, MD, MPH, ABFM, ABOIM
Presenter

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