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FEMME (Female Estrogen Menopause Mind and Energy) study: The interaction between diabetes and estradiol on human brain metabolism in postmenopausal women

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Objective: To determine whether the 8-week administration of transdermal 17 β -estradiol affects the glucose and ketone body uptake to the brain and cognitive performance in postmenopausal women with and without type 2 diabetes.

Background: Type 2 diabetes (T2D) affects an estimated 26% of people over the age of 65 and increases their risk for dementia. Research suggests that metabolic dysregulation in T2D and insulin resistance may raise the risk of dementia by altering substrate use in bioenergetic pathways to rely less on glucose and more on ketone bodies. At the same time, emerging epidemiological studies supported by work in animal models suggest that estrogen levels may impact these pathways and interact with T2D to elevate the risk for dementia in postmenopausal women.

The primary aim of this study is to test the premise of the theory of the healthy cell bias of estrogen action in vivo in humans. The healthy cell bias theory hypothesizes that estradiol has beneficial effects in healthy cells but can have deleterious effects on cells that are affected by diseases such as T2D. Here, we propose to test these effects in humans by using dual-tracer positron emission tomography (PET) to assess whether estrogen affects the uptake of glucose and ketone bodies differently in women with and without T2D.

Study Design: Postmenopausal women aged 65-80 years old will be recruited, 10 with T2D and 10 without from the region of Forsyth County, North Carolina. Participants will receive 0.075 mg/day of transdermal 17 β -estradiol delivered via a Climara patch for 8 weeks. Participants are expected to take 14-18 weeks (study will last 24-36 months) to complete all study visits. Estrogen levels will be measured on 9-11 days after estrogen administration begins to titrate levels as needed to attain a circulating level of 50-100pg/ml for each woman. Patches will be changed weekly. Dual-tracer PET scans measuring uptake of glucose and ketone bodies will be acquired before and after estrogen administration, along with brain MRI and cognitive testing. This abstract lays out the study design for this new trial; we anticipate presenting results at future Women's Health Research Day events.

Funded by: National Institute on Aging (NIA)