

A Review -Menopause, Cognition and Dementia

Ria Memoria, *Dharmendra Singh Rajput

Department of Pharmacy Practice, Indubhai Patel College of Pharmacy and Research Centre, Dharmaj, Anand, Gujrat-388430, India

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*Corresponding Author:
Email:
drrajput00@gmail.com.

ABSTRACT

There is increasing evidence that menopausal changes can have an impact on women's cognition and potentially, the future development of dementia. In particular, the role of reduced levels of estrogens in postmenopausal changes has been linked to an increased risk of developing dementia in observational studies. Not surprisingly, this has led to several clinical trials investigating whether postmenopausal hormone replacement therapy can potentially delay/avoid cognitive changes and subsequently, the onset of dementia. However, the evidence of these trials has been mixed, with some showing positive effects while others show no or even negative effects. Based on the current evidence, we conclude that previous approaches may have used a mixture of women with different genetic risk factors for dementia which might explain these contradicting findings. Therefore, it is recommended that future interventional studies take a more personalized approach towards hormone replacement therapy use in postmenopausal women. By taking into account the women's genetic status for dementia risk

Keywords: Cognition, 'critical window' hypothesis, dementia, Estrogens, menopause, hormone replacement

Introduction

Dementia is one of the most prevalent diseases for ageing societies worldwide. According to the World Health Organisation report (2015), 47.5 million people worldwide have dementia and there are 7.7 million new cases annually [1]. Historically, dementia has been seen as a disease of old age, with age being the greatest risk factor for dementia [2:4].

However, recent evidence suggests that pathophysiological changes leading to dementia can occur up to 20 years before the presentation of clinical symptoms [5:6], which has stimulated an urgent need to investigate how several demographic and life-course factors influence the risk of pathologically induced cognitive decline [3]. In particular, sex-related differences in neural anatomy are emerging as an important factor for both the development and treatment of dementia [2:7]. The risk for dementia appears to differ for men and women throughout the ageing process [8], with women showing an increased risk for dementia shortly after menopause [9]. These findings dovetail with women commonly reporting a 'brain fog' descending after menopause, which might be the first indication of increased dementia risk [7:10]. Nonetheless, the

relationship of menopause-induced cognitive changes and risk of dementia is still under exploration, with previous studies offering conflicting findings to date. The aim of this review is to explore the literature investigating the link between menopause, cognition and dementia. In this review, we will first highlight the current evidence for the relationship between cognition and menopause before exploring the evidence for an association between dementia and menopause. We conclude by outlining potential future directions based on the reviewed evidence.

Literature Review

Cognition and menopause: The occurrence of cognitive changes during menopause is clinically a very common observation, with many subjective reports of 'brain fog' during the menopausal transition, affecting cognitive performance in everyday life [11]. In particular, individuals suffer from impairments to their attention, processing speed and memory, which subsequently manifest as lack of focus, sluggishness and forgetfulness as some of the most common symptoms [10:12]. For example, cross-sectional findings from the Study of Women's Health Across the Nation in a large cohort of women (n ¼ 16,065) aged between 40 and 55 years

showed that 31% of premenopausal women reported increased forgetfulness which increased to 41% in postmenopausal women [13:14]. The contribution of other demographic and lifestyle factors on cognitive performance was not explored. Longitudinal studies have corroborated these cross-sectional changes in cognition, with women reporting worsening cognitive performance from pre to post-menopause [12:15:16]. Importantly, these subjective reports of altered cognitive performance were further supported by more objective cognitive testing, which have shown that premenopausal women perform better than postmenopausal women on neuropsychological testing [17], although the sample sizes for such studies are too limited to draw any definite conclusions at this stage. The reported cognitive changes during menopause have implicated a potential role for hormones (in particular, estrogen) on cognition [15:18]. Specifically, changes in the levels of estrogen as well as expression of estrogen receptor genes (e.g. ESR1, ESR2) have been shown to have an effect on cognition during menopausal transition [10:11] and ageing, respectively [19:20]. This should be not surprising, as estrogen is well known to have strong effects on brain function and integrity, in addition to its reproductive function. For example, estrogen has been shown to have a key role in regulating glucose metabolism in the brain [21]. Glucose metabolism is directly linked to improved cognition; hence, a reduction in the provision and potential uptake of glucose in the brain as a result of lower estrogen levels might partially account for the observed changes in cognitive performance post-menopause [21:22]. Similarly, estrogen has been shown to have significant neurotrophic factors [23:24], thereby impacting on neurogenesis and homeostatic brain function [25], which further highlights the role of this female sex hormone in brain health. Most importantly, estrogen also functions in the metabolism of acetylcholine, one of the main neurotransmitters critical for attention and memory processes [26]. Hence, the deficits, specifically in attention

and memory, post-menopause might potentially be linked to this hormonal-neurotransmitter transaction, although such interactions have to date only been shown in animal models [25]. Clearly, future investigations exploring this role of estrogen towards acetylcholine and cognition, in particular on a longitudinal level, are needed to determine the dynamics of the genotypic and neurotransmitter interactions over long time periods. On a more mechanistic level, several clinical trials involving hormone replacement therapies (HRTs) in postmenopausal women have examined cognitive performance as a secondary outcome measure [27:29]. However, the results from these trials have so far been inconsistent, with some trials showing beneficial effects for cognitive performance, whilst others show no or even deleterious effects on cognitive performance in postmenopausal women [30:33]. These findings have led to the emergence of a 'critical window' hypothesis [12], which states that the HRT can have a positive impact on cognition in pre- and perimenopausal women (up until the age of 60 years when dementia risk is small), but might have a negative effect on cognition in postmenopausal women [34]. However, it should be noted that null/negative effects of HRT on female cognition are observed particularly among women with a heightened genetic vulnerability to developing dementia. In fact, a recent review suggests [35] that an incomplete understanding of the interactions between drugs and genotype that are not considered for in clinical trials might explain some of the controversial results of HRT trials on cognition.

Dementia and menopause: There is currently a large body of studies and public health data showing that incidences of dementia are higher in women than in men [36]. Until recently, the difference in incidence rates was regarded as a collateral effect of women living on average longer than men [2]. This theory is consistent with age

being a major risk Post Reproductive Health 0(0) factor for dementia, and hence aged women suffer significant cognitive decline and thus a higher incidence rate of dementia [3:4]. However, more recent evidence highlights that even when controlling for survival rates in men and women, the increased risk for women persists [8]. Moreover, from a diagnostic perspective, attention and mnemonic changes in cognition that are primarily reported in post-menopausal women are also considered key clinical symptomology in the diagnostic work-up of patients presenting at dementia clinics [12]. Clearly, this evidence raises the question as to whether hormonal changes during the menopause potentially trigger a pathophysiological cascade for Alzheimer's disease (AD) [9]. Already, this notion has recently found strong support by a large meta-analysis of data from over 50,000 women across multiple studies [37]. The study reported that women have a particularly high risk of developing dementia directly in the years following the menopause compared to men.

The effectiveness of HRT in younger vs. older individuals suggests the more carefully controlled HRT trials are needed in future to truly establish if HRT started at an earlier age is a preventative measure for dementia. Finally, there is sufficient evidence to suggest that the role of genetic information should be considered when looking at the menopause-dementia link, thereby increasing the complexity of this relationship [35:53]. The main recessive genetic risk for dementia is the apolipo protein epsilon 4 allele (APOE e4), with heterozygous and homozygous carriers of the APOE e4 genotype harbouring a 4-fold to 12-fold increase risk of AD, respectively [27]. In particular, several studies have shown that female APOE e4 carriers in particular have a significantly increased risk for dementia [5]. Interestingly, the APOE genotype [54] is closely linked to estrogen mechanisms [36], in particular for the lipid metabolism that both pathways are involved in. Importantly, clinical trials have shown that HRT

protective mechanisms towards cognitive decline interact with APOE genotype [12:53]. More specifically, studies have shown that female APOE e4 carriers, who are vulnerable to AD, might benefit from HRT to reduce cognitive decline and potentially the onset of dementia [4:12]. However, so far, there have been very few menopause studies and trials specifically for APOE genotyped women to explore this relationship, in particular towards the 'critical window' hypothesis [27].

Results and Discussion

Taken together, there is increasing evidence for not only a correlational, but also a causal link between menopausal hormone changes and cognition as well as dementia, which has so far been under-explored in the literature. Despite the exciting findings discussed, it emerges that there is complex interaction between menopausal stages, HRT and genetic status (in particular for the APOE genotype) which appears to underlie cognitive deficits and potentially the onset of incipient dementia. In particular, the specific biological mechanisms which link estrogen to cognitive changes and incipient dementia require further investigation. In this regard, the impact of genetic risk factors, such as APOE or estrogen receptors encoded by ESR1/2 genes, seems to be critical to our understanding of the risk profile of women for developing dementia across menopausal stages. Delineating those contributions might help identify women who are at a higher risk for dementia post-menopause, based on their genotype status. This would enable the designing of much more targeted longitudinal and interventional studies for such women, who are potentially at the highest risk of cognitive decline and dementia. In turn, this might also reduce the admixture of women in clinical trials to increase the statistical power for interventions and reduce the outcome variability. Furthermore, on the cognitive testing side, it is recommended that a more systematic approach be adopted

for testing cognitive performance in menopausal women objectively. In particular, more detailed and specific tests to detect potentially incipient dementia processes would be beneficial, as currently most studies and trials use crude cognitive screening tests. Of relevance in this regard might be novel, more dementia pathology-specific tests in spatial navigation, which have been shown to be related to entorhinal cortex integrity and underlying amyloid/ tau pathology [38]. This would allow the delineation of more general cognitive effects of menopausal hormonal changes from dementia-specific ones, again informing future clinical trials. Finally, the identification of such specific menopausal phenotypic and genotypic changes would allow a more personalized approach to identify women 'at-high-risk' of developing dementia, which in turn would allow earlier treatment with a potential to alleviate or even delay the onset of the disease.

References

- Prince M, Wimo A, Guerchet M, et al. World Alzheimer Report 2015 the global impact of dementia: an analysis of prevalence, incidence, cost and trends. London: Alzheimer's Disease International (ADI), 2015.
- Kolanowski AM, et al. Gender differences in factors associated with delirium severity in older adults with dementia. *Arch Psychiatr Nurs* 2014; 28: 187–192.
- Castellani RJ, Rolston RK and Smith M. Alzheimer disease. *Dis Mon* 2011; 56: 1–60.
- Maki PM and Henderson VW. Hormone therapy, dementia, and cognition: the Women's Health Initiative 10 years on. *Climacteric* 2012; 15: 256–262.
- Fleisher AS, Chen K, Quiroz YT, et al. Florbetapir PET binding of amyloid- β deposition in the presenilin 1 E289A autosomal dominant Alzheimer's kindred; a cross-sectional study. *Lancet Neurol* 2012; 11: 1057–1065.
- Reiman EM, Quiroz YT, Fleisher AS, et al. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E2804 kindred: a case-control study. *Lancet Neurol* 2012; 11: 1048–1056.
- Maki PM and Henderson VW. Cognition and the menopause transition. *Menopause* 2016; 23: 803–805.
- Walter A, et al. Sex and gender differences in the causes of dementia: a narrative review. *Maturitas* 2014; 79: 196–201.
- Berglund J. A time of forgetting: menopause may hold a key to understanding the development of Alzheimer's disease. *IEEE Pulse* 2018; 9: 19–21.
- Woods NF, Mitchell ES and Adams C. Memory functioning among midlife women: observations from the Seattle Midlife Women's Health Study. *Menopause* 2000; 7: 257–265.
- Weber MT, Maki PM and McDermott MP. Cognition and mood in perimenopause: a systematic review and metaanalysis. *J Steroid Biochem Mol Biol* 2013; 142: 90–98.
- Davey DA. Alzheimer's disease, dementia, mild cognitive impairment and the menopause: a 'window of opportunity'? *Women's Health* 2013; 9(3): 279–290.
- Bromberger JT, Kravitz HM, Chang YF, et al. Major depression during and after the menopausal transition: study of Women's Health Across the Nation (SWAN). *Psychol Med* 2011; 41: 1879–1888.
- Vega JN, Zurkovsky L, Albert K, et al. Altered Brain connectivity in early postmenopausal women with subjective cognitive impairment. *Front Neurosci* 2016; 10: 433.
- Ryan J, et al. Impact of a premature menopause on cognitive function in later life. *BJOG* 2014; 201: 1729–1739.
- Burger HG, Hale GE, Robertson DM, et al. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. *Hum Reprod Update* 2007; 13: 559–565.
- Huang J, Bai F, Yang X, et al. Identifying brain functional alterations in postmenopausal women with cognitive impairment. *Maturitas* 2015; 81: 371–376.
- Pike CJ, Carroll JC, Rosario ER, et al. Protective actions of sex steroids. *Front Neuroendocrinol* 2009; 30: 239–258.
- Rettberg JR, Yao J and Brinton RD. Estrogen: a master regulator of bioenergetic systems in the brain and body. *Front Neuroendocrinol* 2014; 35: 8–30.
- Rocca WA. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Melton Neurol* 2007; 69: 1074–1083.
- Brinton RD. The healthy cell bias of estrogen action: mitochondrial bioenergetics and neurological implications. *Trends Neurosci* 2008; 31: 529–537.
- Wang Y and Brinton RD. Estrogen regulation of mitochondrial respiration is cell type and ER subtype specific. *Alzheimer's Dementia* 2017; 13: P665–P666.
- Spencer JL, Waters EM, Romeo RD, et al. Uncovering the mechanisms of estrogen effects on hippocampal function. *Front Neuroendocrinol* 2008; 29: 219–237.
- Brann DW, Dhandapani K, Wakade C, et al. Neurotrophic and neuroprotective actions of estrogen: basic mechanisms and clinical implications. *Steroids* 2007; 72: 381–405.
- Emmens CW, Macintosh FC and Richter D. Oestrogens and acetylcholine. *J Physiol* 1943; 101: 460–464.
- Markowska AL and Savonenko AV. Effectiveness of oestrogen replacement in restoration of cognitive function after long-term oestrogen withdrawal in aging rats. *J Neurosci* 2002; 22: 10985–10995.
- Depypere H, Vierin A, Weyers S, et al. Alzheimer's disease, apolipoprotein E and hormone replacement therapy. *Maturitas* 2016; 94: 98–105.
- Hodis HN, Mack WJ, Shoupe D, et al. Methods and baseline cardiovascular data from the early versus late intervention trial with estradiol testing the menopausal hormone timing hypothesis. *Menopause* 2015; 22: 391.
- Woods NF, et al. Symptoms during the perimenopause: prevalence, severity, trajectory, and significance in women's lives. *Am J Med* 2005; 118: 14–24.
- Espeland MA, et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. *JAMA Intern Med* 2013; 173: 1429–1436.
- Gleason CE, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEOPS-cognitive and affective study. *PLoS Med* 2015; 12: 1833.
- Henderson VW, et al. Cognitive effects of estradiol after menopause. *Neurology* 2016; 87: 699–708.
- Intiaz B, et al. Postmenopausal hormone therapy and Alzheimer disease. *Neurology* 2017; 88: 1062–1068.

34. Ratka A. Menopausal hot flashes and development of cognitive impairment. *Ann N Y AcadSci* 2005; 1052: 11–26.
35. Ferretti MT, et al. Sex differences in Alzheimer disease – the gateway to precision medicine. *Nat Rev Neurol* 2018; 14: 457–469.
36. Che'ne G, et al. Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimer's Dementia* 2015; 11: 310–320.
37. Neu SC, et al. Apolipoprotein E genotype and sex risk factors for Alzheimer disease: a meta-analysis. *JAMA Neurol* 2017; 74: 1178–1189.
38. Coughlan G, et al. Spatial navigation deficits – overlooked cognitive marker for preclinical Alzheimer disease? *Nat Rev Neurol* 2018; 14: 496–506.
39. Xu H, Gouras GK, Greenfield JP, et al. Oestrogen reduces neuronal generation of Alzheimer b-amyloid peptides. *Nat Med* 1998; 4: 447.
40. Casadesus G, Webber KM, Atwood CS, et al. Luteinizing hormone modulates cognition and amyloidb deposition in Alzheimer APP transgenic mice. *BiochimBiophysicaActa (BBA) – Mol Basis Dis* 2006; 1762: 447–452.
41. Petanceska SS, Nagy V, Frail D, et al. Ovariectomy and 17b-estradiol modulate the levels of Alzheimer's amyloid b peptides in brain. *Neurology* 2000; 54: 2212–2217.
42. Takeda S and Matsuzawa T. Age-related brain atrophy: a study with computed tomography. *J Gerontol* 1985; 40: 159–163.
43. Lethaby A, Hogervorst E, Richards M, et al. Hormone replacement therapy for cognitive function in postmenopausal women. *Cochrane Database Syst Rev* 2008; 23: 3122.
44. Gibbs RB and Gabor R. Oestrogen and cognition: applying preclinical findings to clinical perspectives. *J Neurosci Res* 2003; 74: 637–643.
45. Jick HZ, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. *Lancet* 2000; 356: 1627–1631.
46. Delanty N and Vaughan CJ. Vascular effects of statins in stroke. *Stroke* 1997; 28: 2315–2320.
47. Yaffe K, Sawaya G, Lieberburg I, et al. Oestrogen therapy in postmenopausal women: effects on cognitive function and dementia. *JAMA* 1998; 279: 688–695.
48. LeBlanc ES, Janowsky J, Chan BK, et al. Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA* 2001; 285: 1489–1499.
49. Hogervorst E, Williams J, Budge M, et al. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in postmenopausal women: a meta-analysis. *Neuroscience* 2000; 101: 485–512.
50. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine oestrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291: 1701–1712.
51. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of oestrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321–333.
52. Fox M, Berzuini C, Knapp LA, et al. Women's pregnancy life history and Alzheimer's risk: can immunoregulation explain the link? *Am J AlzheimersDis Other Demen* 2018; 33: 516–526.
53. Buckley RF, et al. Sex, amyloid, and APOE e4 and risk of cognitive decline in preclinical Alzheimer's disease: findings from three well-characterized cohorts. *Alzheimer's Dementia* 2018; 4: 1193–1203.
54. Corder EH, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993; 261: 921–923.
55. Shanmugan S and Epperson CN. Oestrogen and the prefrontal cortex: towards a new understanding of oestrogen's effects on executive functions in the menopause transition. *Hum Brain Mapp* 2014; 35: 847–865.
56. Voytko ML, Murray R and Higgs CJ. Executive function and attention are preserved in older surgically menopausal monkeys receiving oestrogen or oestrogen plus progesterone. *J Neurosci* 2009; 29: 10362–10370.