

# Hormones and dementia – a comparative study of hormonal impairment in post-menopausal women, with and without dementia

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**Context:** Women seem to be more vulnerable to dementia, particularly Alzheimer's disease (AD), than men. There is controversy among studies correlating estrogen deficit to cognitive impairment. Because of the sudden drop of estrogens in menopause, this hormonal deficit could represent one of the risk factors for the larger incidence and prevalence of AD in post-menopausal women.

**Rationale:** We therefore wanted to find out if post-menopausal women with dementia, or even in a prior stage, mild cognitive impairment (MCI), would have a more significant deficit of estrogens than post-menopausal women without dementia, or any other type of cognitive problem.

**Objectives:** The aim of this study was to detect possible differences of the sex hormone levels among post-menopausal women, simultaneously affected by MCI or dementia, in comparison with a control group without cognitive impairment.

**Design, setting, and participants:** A small, multicenter, prospective study was performed on 82 post-menopausal women (41 cases, 41 controls), aged 45–81 years, to investigate their sex hormone balance. The diagnosis of dementia was made according to ICD 9 or 10 and DSM III-R or IV appropriate to the time interval. The diagnosis of probable AD followed the NINCDS-ADRDA criteria. MCI met the Paquid-study criteria. Blood was analyzed in qualified centers for LH, FSH, and 17- $\beta$ -estradiol. All women went through a thorough psychiatric examination and those with a suspected hormonal impairment were examined by a gynecologist.

**Results:** 15 cases (36.6%) had impaired hormonal function, compared with 8 controls (19.5%). Of the 15 cases with hormonal impairment, 9 had MCI.

**Conclusions:** These preliminary data stress a considerable difference between the sex hormone status of these two populations, showing a tendency towards a more accentuated estrogen deficit linked to cognitive deficit. Enlarging the sample and following the evolution could bring more interesting data.

**Keywords:** dementia, cognitive impairment, post menopause, estrogens

## Background

The intriguing fact that women are far more affected with Alzheimer's disease (AD) than men (Buckwalter et al 1993; Lamberts et al 1997; Hofman and Launer 1998; Gelfand et al 2001) led us to think about risk factors specifically linked to gender (Henderson 2000). Again women seem to have their own protective factors, which give them a longer life expectancy than men, with a prevalence of 5%–7% more over the age of 65 years and of up to 50% more over the age of 85 (Evans 1989; Jorm 1998). But what really differs between both genders are the sex hormones.

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There are several known risk factors other than gender for AD (Snowdon 1997; Friedland 1998), namely, heredity, old age, low level of education, and head injury, as well as the disease risk modifier *e4* allele for the apolipoprotein E (ApoE).

The first clinical signs of the disease appear around 60–70 years, by the time women are already post-menopausal. Men and women both produce estrogen, but men do not suffer such an abrupt reduction of this hormone as do women (Henderson 2000).

The timing of production of estrogens differs between the two genders. Men start to produce testosterone in the testicles between weeks 16 and 18 of fetal life. It migrates to the brain to be aromatized into estrogen. And because there is a regular and strong production of testosterone in the normal male, estrogen quantities are also substantial in the male brain, even more than in the female brain. Testosterone production in men does not start to slow down until they reach their eighties, by the time they just begin to be affected by AD in the same proportion as women of their age.

Estrogens and progestagens are the main ovarian steroids, although the ovaries produce also a small quantity of the “male” testosterone.

During the normal menstrual cycle two gonadotropins from the pituitary gland induce the production of estrogen in the ovaries, by the luteinizing hormone (LH) in the thecal cells and by the follicle stimulating hormone (FSH) in the granulosa cells. The most important circulating estrogen is estradiol, which together with estrone and estriol builds the main estrogens (Lobo 1999). Estradiol is transformed into estrone by the liver and, as well as estrone, can convert into the less active estriol.

Estrogens are derived from cholesterol via precursor androgens: 17- $\beta$ -estradiol, estrone, and estradiol. Estradiol is the most important. Estradiol peaks prior to (in the follicular phase) and after (in the luteal phase) ovulation. In the luteal phase progesterone peaks, too.

The targets for estrogen are the reproductive tissues and, more importantly, the brain (McEwen 1997), followed by bone, vascular endothelium, and skin.

Testosterone converts into estradiol in neurons and in astrocytes possessing the enzyme aromatase. It is through large amounts of estrogen that the male fetus undergoes masculinization.

Basic research shows that estrogens have a receptor protein in the brain, which appears in two forms:  $\alpha$ , mainly in the hypothalamus, and  $\beta$ , throughout a great part of the brain (Garcia-Segura 2003). They act in the neurons and in

the glia. In the hypothalamus they inhibit apoptosis; in the glia they interact with a growth factor, insulin-like growth factor 1 (IGF-1), to give neuroprotection after brain lesion. They also decrease the expression of the levels of  $\beta$ -amyloid in the brain of castrated female rats and in the plasma of humans (Petanceska et al 2000; Almeida 2004).

Estrogens play a role in hippocampal neuronal long-term potentiation, in reinforcing memory, and also act against the effects of some memory-impairing drugs such as benzodiazepines and anticholinergics. They also have an action, although apparently weak, in reducing the neuronal response to oxidative stress (Cordoba 1997; Gibbs 1998; Sawada 1998), and improving regional cerebral blood flow (Ohkura et al 1994; Belfort et al 1995). It is likely that the results of animal studies on the correlation of endogenous estrogens with cognitive performance do not agree with those on humans (Daniel et al 1997; Packard and Teather 1997a, 1997b), in which the effect on cognitive variables such as explicit memory and visual-spatial skills is very modest (Polo-Kantola et al 1998; Resnick 1997). More than 50 years of studies on humans have shown that menopausal estrogen replacement therapy (ERT) enhances short- and long-term memory and increases capacity for learning paired associations but does not improve visual memory (Sherwin 1988, 1997).

There are also studies reporting the influence of estrogens on the suppression of the activity of monoaminooxidase and on the increase of serotonin blood levels in menopause (Luine and McEwen 1975; Gonzales and Carrillo 1993).

Testosterone, but not estrogen, should also play a role. Gelfand blocked the enzyme aromatase and found that human primary neurons were protected by testosterone through the androgen receptor (Gelfand et al 2001).

Menopause afflicts a large percentage of women with hot flushes, day and night sweats, insomnia, vulvar and vaginal dryness, fatigue, slowness, and forgetfulness, among other symptoms. Excluding those women who already had previous episodes of depression, there is usually no depression in the sense of a psychiatric disease. Some feelings of sadness or solitude are often reinforced by preretirement, and or the so called “empty nest syndrome”, and some women have also to face the burden of caring for disabled parents.

Symptoms appear insidiously. Though the flushes are different from usual, they often announce themselves by a most discrete but sudden and unrelated sense of helplessness, like an epileptic aura, almost always unnoticed, to be

followed after approximately one minute by a crescendo hot flush with unusual sweats. These are unusual because they peculiarly start at less common sites, namely on the lower legs, on the back of the knees, on the gluteal folds, on the upper site of the forearms, and on the scalp, leaving the body quite exhausted, accompanied by a uncomfortable feeling of embarrassment. Since this may happen many times in an hour, always out of control, concentration and work rhythm tend to slow down, and soon an uncomfortable sense of fatigue and irritation takes place. Such symptoms begin to be treated by many gynecologists, psychiatrists, and general physicians with serotonin reuptake inhibitors, which often induce, or reinforce, loss of libido.

While the benefits of estrogens offer little evidence for the treatment of an established dementia (Yaffe 2001), their use as a preventive factor is still very controversial (Mulnard et al 2000). Some authors suggest that in order to prevent probable dementia, women must initiate hormone therapy around menopause (Grodstein et al 2002; Resnick and Henderson 2002).

By far the largest continuing study is the Women's Health Initiative (WHI) launched in 1991 to investigate the major causes of death and disability for a period of 8–12 years, in 161 000 post-menopausal women (50–79 years), enrolled between September 1993 and December 1998 in the US (WHISG 1998; Fouad et al 2004). In the clinical trial arm, 27 347 women, aged 50–79 years, were assigned to the hormone replacement component in 1996. From this section the Women's Health Initiative Memory Study (WHIMS) was formed, enrolling more than 7500 women aged 65 or older, without dementia. Part of the study (the combined hormone therapy group, with a total of 2229 women randomized to treatment with 0.625 mg/day of conjugated equine estrogen plus 2.5 mg/day of medroxyprogesterone acetate or placebo) was discontinued in 2002, 5.6 years after the start (less than 4 years before the planned end), because of increased risk of breast cancer, heart disease, stroke, and venous thromboembolism (Writing group for the WHI investigators 2002; Schneider 2004), despite showing decreased risks for hip fracture and colon cancer.

The first WHIMS results (Shumaker et al 2003) reported an increased risk of dementia with combined estrogen and progestin therapy (Prempro™) without benefit for mild cognitive impairment (MCI) or global cognition. Similar adverse effects were reported by the Heart and Estrogen/Progestin Replacement Study (HERS II) (Grady et al 2002; Hulley et al 2002), and by the Million Women Study (MWS 2003).

The estrogen-alone group (3000 women) (Shumaker et al 1998) went on for two more years to be stopped in February 2004, because of increased risk for stroke (decreased risk for hip fracture was also reported). The results of the therapy were published as having an adverse effect on cognition, an effect greater in women with initial low cognitive levels (Espeland et al 2004; Schneider 2004).

Taking a critical look at these results (NIA), the risk of dementia in the combined therapy group had no statistical significance, the absolute risk being only 23 more cases per 10 000 women each year (12 extra cases of dementia for each 10 000 women each year) (Shumaker et al 2003). In other words, 40 out of 2229 women developed dementia during the 5.6 years in the Prempro group while 21 out of 2303 women developed dementia in the placebo group during the same period (Alzheimer's Association 2003).

Also the differences between the estrogen-alone and the placebo groups of WHIMS, although statistically significant, were not considered clinically relevant for overall cognitive abilities. The increased risk of dementia was not statistically significant (Rapp et al 2003; Shumaker et al 2003; Espeland et al 2004). Another criticism was that the findings could be different for lower doses or other types of hormone replacement therapy (HRT) (Editorials BMJ 2002). In fact, the US Food and Drug Administration (FDA) approved in March 2003 a lower daily dose tablet of Prempro (0.45 mg estrogens instead of 0.625 mg and 1.5 mg progestin instead of 2.5 mg) for the specific symptoms of menopause in women with uterus (because progestin lowers the risk of having uterine problems), but not recommending its use for the prevention of heart disease, heart attacks, or strokes (FDA 2003).

It should be noted that for a white, caucasian woman the estimated cumulative absolute risk of death between the ages of 50 and 94 years is 31% from coronary heart disease, 2.8% from breast cancer, and 2.8% from hip fracture (Brinton and Schairer 1997).

A meta-analysis showed that the increased risk of breast cancer affects only women who consume alcohol (5 g or more daily) along with estrogen (Longnecker et al 1988; Colditz et al 1990; Gapstur et al 1992). In a post-menopausal woman who drinks alcohol, the blood level of estradiol goes up by about 300% (Ginsburg et al 1996).

Most women enrolled in WHIMS were much too old for a post-menopausal hormonal study (Schneider 2004). Some women had also already taken hormones, and the possibility remains that some women who were described as having developed MCI or dementia during the trial already had it, subclinically, at the start point.

Based on the WHIMS results, NIA recommended in March 2004 that either estrogens alone or combined with progestin should be prescribed for older women to maintain or improve cognitive function, not directly addressing decisions about the short term use of combination therapy by younger women to relieve symptoms of menopause (NHLBI 2004; WHI 2004).

Other trials found similar results to those of WHIMS for the cognition (Henderson 2000; Mulnard et al 2000; Wang et al 2000). There is evidence for and against the effects of estrogen on cognition being dose- and age-related (Yaffe et al 1998b; Le Blanc et al 2001; Geerlings et al 2003; Almeida and Flicker 2005). A few studies report a protective action against developing AD, probably as a dose-related phenomenon (Tang et al 1996; Kawas et al 1997; Lerner et al 1997).

The Alzheimer's Association also expressed a sceptical opinion, considering the actual individual risk for dementia in the WHIMS study very small and reinforcing that age would still be the major individual risk factor for dementia (Albert 2003).

Before WHIMS was launched there were already other robust studies. The Baltimore Longitudinal Study (Kawas et al 1997) reported a 54% reduced risk for AD among postmenopausal women who had ever taken ERT. Paganini-Hill et al (1994), who conducted by far the largest ERT study before WHI, found that retired women who also had ever taken ERT developed one third less AD.

In a perimenopausal follow-up of 5 years, Tang et al (1996) found that those women who were already on ERT had a decrease of 50% in developing AD.

But in a group of women already with mild to moderate AD, some on unopposed estrogens and some on combined hormones, the estrogen-alone subgroup showed cognitive decline and the combined therapy group failed to present cognitive benefits (Mulnard et al 2000).

All these results are in favor of an action of HRT for menopause more as a factor of prevention or protection for AD or related dementias rather than a therapy once the disease is established.

## Methods

The study was conducted simultaneously in three different centers by a geriatric psychiatrist with extensive experience in dementia, namely in the outpatient clinic for demented patients at a university hospital (neurology department); in the psychogeriatric sector of a clinical center, and in one community medical center (general practice and women health sectors), all in the same locality.

The study sample consisted of community-dwelling women who came to their regular appointments and consented to be enrolled. Out of 133 screened women, 13 did not meet the criteria and 38 were excluded because of dropout or other reasons. Exclusion criteria for cases and controls were psychiatric or physically significant diseases, such as depression, epilepsy, cancer, stroke, uncontrolled hypertension, diabetes, thyroid disease, or any other significant metabolic disorder or serious disease (all women had recently been to their family physician), as well as current or previous treatment with HRT or anti-cholinesterases.

All women went through a thorough psychiatric examination by one and the same psychiatrist with considerable experience in dementia, and were screened using the Mini Mental State Examination (MMSE) (Folstein et al 1975), validated for the Portuguese population, and/or the Information-Memory-Concentration Test (Blessed et al 1968); the Global Deterioration Scale (GDS) (Reisberg et al 1982); the Blessed Dementia Scale (Blessed et al 1968); Hamilton scales for depression (Hamilton 1960) and for anxiety (Hamilton 1969); and the Hachinski ischemic scale (Hachinski et al 1975). Cut off points of the Portuguese-validated MMSE are:  $\leq 15$  for illiterate,  $\leq 22$  for those with 1–11 years of school education, and  $\leq 27$  for those with more than 11 years of school education.

A sex hormone profile was requested from all women, to be performed in highly qualified laboratories. Required was: 17- $\beta$ -estradiol, FSH, LH, and prolactin. The main laboratory criteria for menopause (chemoluminescence method) were: FSH: 25.0–145 mUI/mL; 17- $\beta$ -estradiol  $< 30$  pg/mL; and LH 18.0–65.0 mUI/mL. 17- $\beta$ -estradiol is the considered the more important estrogen in this context (Lobo 1999).

Only cases were included who met the criteria for dementia according to DSM-III R or DSM-IV (APA 1987, 1994), or ICD-9 or ICD-10 (WHO 1975, 1992), depending on the time interval; for AD according to the ADRDA-NINCDS (McKhann et al 1984); and for MCI according to the Paquid study criteria (Dartigues et al 1991a, 1991b, 1992; Barberger-Gateau et al 1992, 1993). GDS scores were 2–7 for cases (mild cognitively impaired to moderate/severely demented), and MMSE according to the above-mentioned cut-off points. Controls GDS scores were 1–2.

Cases underwent a structured interview in the context of the regular psychiatry–psychogeriatric appointment, some of them with help of the caregiver. Each case with menopausal symptoms and biochemical hormone deficit

**Table 1** Average age of controls and cases

	Average age (years)	MCI	DEM	AD
Controls (n = 41) (42–79)	60.3			
Cases (n = 41) (45–87)	67.4	63.8	71.2	69.8

**Abbreviations:** AD, Alzheimer's disease; DEM, undiagnosed dementia; MCI, mild cognitive impairment.

agreed to be evaluated and examined by a gynecologist, who performed a gynecological observation, requested mammography and mammary ultrasound, and carried out the pap cell test. After having met the clinical diagnosis of estrogen deficit, the gynecologist informed the women, in the indicated cases, on the risks and advantages of HRT.

Controls without any cognitive impairment were all selected either from medicine (general practice) or gynecology. Forty-one cases and 41 controls were enrolled between 1994 and 1998, aged 42–87 years, mean 63.8 years, more exactly 67.4 years for the cases (45–87 years) and 60.3 years for the controls (42–79 years) (Table 1).

## Results

Among the cases the following diagnoses were found. MCI: 15 cases = 36.5%; AD: 11 cases = 26.8%; uncharacterized dementia (DEM): 10 cases = 24.3%, frontal dementia (FD): 2 cases = 4.8%; vascular dementia (VD): 1 case = 2.4%; Parkinson's dementia (PD): 1 case = 2.4%; alcohol dementia (AlcD): 1 = 2.4% (Table 2).

Most of the cases belonged to MCI, AD, and DEM. MCI with a mean age of 63.8 was the youngest group. It would obviously be interesting to know how these MCI and DEM cases would be later distributed, as the disease progresses and the diagnosis becomes more clear.

According to the conclusions of the gynecologist, there were 15 cases with estrogen deficit (36.6%) compared with only 8 controls (19.5%) (Table 3). The distribution of these

**Table 2** Diagnosis of cases (n = 41)

Diagnosis	n (%)
MCI	15 (36.5%)
AD	11 (26.8%)
DEM	10 (24.3%)
FD	2 (4.8%)
VD	1 (2.4%)
PD	1 (2.4%)
AlcD	1 (2.4%)

**Abbreviations:** AD, Alzheimer's disease; AlcD, alcohol dementia; DEM, undiagnosed dementia; MCI, mild cognitive impairment; FD, frontal dementia; VD, vascular dementia; PD, Parkinson's dementia.

**Table 3** Women with hormonal deficit

	With hormonal impairment
Controls (n=41)	8 (19.5%)
Cases (n=41)	15 (36.6%)
MCI	9 (21.9%)
DEM	3 (7.3%)
AD	2 (4.8%)
AlcD	1 (2.4%)

**Abbreviations:** AD, Alzheimer's disease; AlcD, alcohol dementia; DEM, undiagnosed dementia; MCI, mild cognitive impairment.

cases with hormonal impairment was: MCI, 21.9%; DEM, 7.3%; AD, 4.8%; AlcD, 2.4% (Table 3).

Most of the cases with estrogen deficit were from the MCI subgroup (9 cases), far more significant than the DEM (3 cases) and AD (2 cases) subgroups. There is evidence from other studies that half or more of these MCI cases decline within few years to AD or related dementia, but a considerable percentage does revert to normal, or near normal, again (Rubin et al 1989; Flicker et al 1991; Ritchie et al 2000).

## Discussion

The results of the present study provide evidence for a tendency for menopausal women with estrogen deficit to present an impairment of cognitive function in the form of MCI or dementia, particularly compared with the controls (36.6%–19.5%), which is in keeping with our initial hypothesis that an estrogen deficit could be a risk factor for AD or even for some other types of dementia.

Our study, although original, has some limitations. It was much too small to be a case control study, had a great disparity of ages, and lacked any other suitable factor (like level of education) that would allow us to match cases with controls (Table 4). It may well be considered that once menopause begins age does not play such an important role in what concerns sex hormone level, and so the age differences would not be important.

The enrolment should also have been bilateral, not mainly from psychiatry–psychogeriatrics but from gynecology, too, which happened only with two women. All women should have been checked by a second experienced psychiatrist or neurologist.

We conclude that elderly women with MCI and dementia tend to show a significant estrogen deficit, particularly when compared with cognitively unimpaired controls. An estrogen deficit may represent an important risk factor for MCI, AD, and even some other types of dementia.

**Table 4** Stratification by age of cases and controls with respective pathology and hormonal impairment

Cases/Age	Pathology	HI	Nr cases with HI per age decile	% cases with HI per age decile	Controls/age	HI	Nr controls with HI per age decile	% controls with HI per age decile
45	MCI	I			42	0		
47	MCI	0			46	0		
51	MCI	I			47	0		
54	MCI	I			47	I		
55	MCI	I			48	0		
57	AD	0			48	0	8	16.66
59	DEM	0			50	I		
59	AD	0	4	50	50	0		
60	MCI	I			51	I		
60	AlcD	I			51	I		
60	DEM	0			53	0		
60	DEM	0			54	0		
61	MCI	0			54	0		
61	FD	0			54	0		
63	MCI	0			55	0		
64	VD	0			57	0		
65	AD	I			58	0		
66	AD	0			59	0	3	25
67	MCI	I			62	0		
67	AD	0			62	I		
69	PD	0			63	0		
69	MCI	0	4	28.57	64	0		
70	DEM	0			64	0		
72	MCI	0			64	I		
72	AD	I			64	0		
73	AD	0			65	0		
73	MCI	I			65	0		
74	DEM	I			65	I		
74	AD	0			67	0		
75	AD	0			67	0		
75	MCI	I			67	I		
76	FD	0			68	0		
76	DEM	0			68	0	4	26.66
77	DEM	I			70	0		
78	MCI	0			71	0		
78	DEM	0			72	0		
78	DEM	0			72	0		
79	AD	0			75	0		
80	DEM	I			76	0		
81	AD	0			77	0		
87	MCI	I	7	36.84	79	0	0	0
Total with HI		15				8		
% total with HI		36.58				19.51		

**Abbreviations:** AD, Alzheimer's disease; AlcD, alcohol dementia; DEM, undiagnosed dementia; MCI, mild cognitive impairment; FD, frontal dementia; HI, hormonal impairment; PD, Parkinson's disease; VD, vascular dementia.

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