Can testosterone replacement decrease the memory problem of old age?

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Summary The world is rapidly ageing. It is against this backdrop that there are increasing incidences of dementia reported worldwide, with Alzheimer's disease (AD) being the most common form of dementia in the elderly. It is estimated that AD affects almost 4 million people in the US, and costs the US economy more than 65 million dollars annually. There is currently no cure for AD but various therapeutic agents have been employed in attempting to slow down the progression of the illness, one of which is oestrogen. Over the last decades, scientists have focused mainly on the roles of oestrogen in the prevention and treatment of AD. Newer evidences suggested that testosterone might also be involved in the pathogenesis of AD. Although the exact mechanisms on how androgen might affect AD are still largely unknown, it is known that testosterone can act directly via androgen receptor-dependent mechanisms or indirectly by converting to oestrogen to exert this effect. Clinical trials need to be conducted to ascertain the putative role of androgen replacement in Alzheimer's disease.
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CAN TESTOSTERONE REPLACEMENT DECREASE THE MEMORY PROBLEM OF OLD AGE?

It is well known that plasma oestrogen levels decline during the menopause in ageing women, but it is debatable whether a similar process takes place in older men in relation to testosterone. Several studies have now confirmed that testosterone levels decline significantly with increasing age in men (see review (1)), although this relative decrease is modest compared with the decrease in oestrogen levels observed amongst perimenopausal women. Ageing men develop clinical signs of hypogonadism such as reduced muscle and bone mass, and

increase in visceral fat; however, not all men become hypogonadal as they age, with some exhibiting peak activity well into old age (see review (2)). Low testosterone levels have also been associated with depression in ageing men, with clinical improvement reported after testosterone supplementation (3). These findings in association with the results from an interesting double-blind, placebo-controlled study which demonstrated that testosterone replacement therapy improves depression as well as verbal and spatial memory in ageing men (4) sparked interest in exploring the possible role of androgen replacement therapy to prevent some of the mental health disorders of later life, including Alzheimer's disease (AD).

The results of several reports indicate that oestrogen replacement therapy decreases the risk of AD in later life (5–11). Oestrogen is known to promote neuronal sprouting (12) and enhance cholinergic activity in the brain (13). In addition, oestrogen lowers plasma apolipoprotein E levels (14), increases cerebral blood flow (15), and activates astrocytes. There is preliminary

evidence that these effects of oestrogen reduce the pathological accumulation of the neurotoxic Alzheimer's β-amyloid (Aβ) peptide, thereby delaying or even preventing the onset of the illness. In addition, oestrogen is known to possess anti-inflammatory (16) and antioxidant properties (17), both of which may decrease Aβ-induced toxicity. Oestrogen has also been reported to favour the non-amyloidogenic processing of Aβ precursor protein (APP) and decreases the formation of intact neurotoxic Aβ peptide (18,19).

Whilst the role of oestrogen in women has received a great deal of scientific attention, there has been only limited interest about the Neuropsychiatric role of androgen in men. Research into the roles of testosterone and cognition has conventionally focused on the association between this gonadal hormone and visuospatial abilities (high- and low-testosterone levels seem to be associated with poorer performance (20)). In addition, there is increasing evidence that testosterone replacement is associated with mood scores and that is use can be an effective adjunct to the treatment of depressive episodes in men and women (see review (21)).

In relation to AD, there are several potential mechanisms by which testosterone may protect against neurodegeneration: prevention of tau protein hyperphosphorylation (one of the neuropathological hallmarks of AD) (22), changes in APP metabolism to preclude Aβ formation (23), increased expression of nerve growth factor (24), reversal of the age-related increases in glial fibrillary acidic protein (often used as an index of neurodegeneration) (25), increased the rate of axonal regeneration via selective alterations of the neuronal cytoskeleton (26), promotion of neurite growth and interneural communication through branching and arborisation (27), synergistic stimulation of protein synthesis in combinations with other cytokines such as insulin growth factor-1 (28), conversion of testosterone to oestrogen (29). In addition, testosterone may also be beneficial through its anti-apoptotic effect (30).

It is now widely accepted that apoptotic cell death is critical in maintaining tissue homeostasis as well as a defence mechanism to remove unwanted and potentially dangerous cells, such as self-reactive lymphocytes, virus-infected cells and tumour cells. Apoptosis is also increasingly being implicated in the pathogenesis of many diverse human diseases including AD (31). At present, there is no direct evidence that testosterone modulates apoptosis pathways in AD, although there is preliminary evidence suggesting that testosterone withdrawal produces an acceleration of germ cell apoptosis at specific stages of the seminiferous epithelial cycle (30). Moreover, testosterone treatment reduces the extent of neuronal cell death following trophic factor withdrawal (32) and adrenalectomy (33). Finally, there is in vitro evidence testosterone favourably attenuates Aβ-medicated apoptosis (34).

We have recently reported that androgen deprivation increases plasma Aβ levels (35) and that these changes may be associated with progressive cognitive decline in humans (36). This finding is consistent with those of a previous report of decreased testosterone levels amongst men with AD (37). Collectively, these results suggest that testosterone use may be of some benefit in the prevention of AD. However, the timing of the hormone replacement therapy is likely to be critical as the gene corresponding to the androgen receptor is located on the X chromosome (38) and chromosome X inactivation increases with increasing age (39,40). Therefore, decreasing amount of androgen receptors are likely to result in cells becoming less responsive to testosterone treatment.

In addition to its potential role in AD, androgen replacement may also be of clinical relevance to the prevention of vascular dementia. With the association of vascular risk factors implicated in AD (see review (41)), the effects of androgen on different lipoproteins is of particular interest as it might explain, in part, the higher prevalence of arteriosclerosis and shorter life span of men than women, and may also shed some light into the possible role of these hormones in the pathogenesis of dementia.

The hormonal regulation of lipid metabolism in men is complex and not well understood. Androgens have been shown to exert a significant influence on lipid metabolism in several different ways. They regulate genes involved in fatty acid and cholesterol synthesis (42), and can influence the activity of lipogenic enzymes and the incorporation of fatty acids into neutral lipids (43). In addition, androgens seem to influence the cellular content of cholesterol and other neutral lipids (44). Testosterone does not affect the rates of apolipoprotein secretion, but increases the concentration of oestrogen required to induce apoCII and apoAI maximally by a mechanism that involves high-affinity androgen receptors (45). In addition, gonadal steroid hormones are lipophilic; therefore, they can potentially intercalate into the bilayer of target cell membranes, hence altering the fluidity and function of the membrane (46).

Similar to AD, low levels of androgen were reported in patients with vascular dementia (47–49) and androgen therapy in these patients was found to improve their ability to perform daily tasks and to decrease emotional disturbances (3,50–53). Testosterone replacement in hypoandrogenic men has a favourable protective effect against premature onset of arteriosclerosis (43). These effects may be mediated through changes to blood pressure (54), vascular smooth muscle potassium channels (55), vascular smooth muscle cell growth (47,56),

and/or through direct stimulation of endothelium-derived nitric oxide (57).

Patients with dementia or cognitive impairment often require hospitalisation (58) or institutionalisation (59) in the later stages of their illness. Mortality rates have also been shown to be higher in persons with severe cognitive impairment (60). As the proportion of elderly people in the population continues to grow, the personal and social burden of cognitive impairment will reach epidemic proportions. The cost of providing adequate healthcare for dementia sufferers and support for their caregivers is substantial, and an effective preventative strategy should contribute to reduce this financial burden. In the USA, the annual cost of AD alone is as high as $90 billion (61). In Australia, it has been estimated that the cost of providing primary community-based services to AD sufferers reaches $10,234 per person per year (62). However, these cost assessments do not take into consideration the quality of life of the sufferers or the emotional burden on relatives and close friends. Clearly, the introduction of effective measures to prevent dementia would have significant clinical, social, and financial implications. In this context, the potential benefits of hormone replacement should not be ignored.

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