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Review

Hormonal changes and their impact on cognition and mental health of ageing men☆

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ABSTRACT

Demographic changes resulting in ageing of the world's population have major implications for health. As men grow older, circulating levels of the principal androgen or male sex hormone testosterone (T) decline, while the prevalence of ill-health increases. Observational studies in middle-aged and older men have shown associations between lower levels of T and poorer mental health in older men, including worse cognitive performance, dementia and presence of depressive symptoms. The role of T metabolites, the more potent androgen dihydrotestosterone (DHT) and the oestrogen receptor ligand estradiol (E2) in the pathophysiology of cognitive decline are unclear. Studies of men undergoing androgen deprivation therapy in the setting of prostate cancer have shown subtle detrimental effects of reduced T levels on cognitive performance. Randomised trials of T supplementation in older men have been limited in size and produced variable results, with some studies showing improvement in specific tests of cognitive function. Interventional data from trials of T therapy in men with dementia are limited. Lower levels of T have also been associated with depressive symptoms in older men. Some studies have reported an effect of T therapy to improve mood and depressive symptoms in men with low or low-normal T levels. T supplementation should be considered in men with a diagnosis of androgen deficiency. Beyond this clinical indication, further research is needed to establish the benefits of T supplementation in older men at risk of deteriorating cognition and mental health.

Contents

Abbreviations: AD, Alzheimer's dementia; AN, anastrazole; ADT, androgen deprivation therapy; APOE ε4, apolipoprotein E ε4 allele; BDI, Beck depression inventory; CES-D, Center for Epidemiologic Studies Depression; DHT, dihydrotestosterone; E2, Estradiol; GDS, Geriatric Depression Scale; Health ABC, Health Aging and Body Composition; HIMS, Health In Men Study; GnRH, gonadotrophin-releasing hormone; LN, levonorgestrel; LH, luteinising hormone; MMAS, Massachusetts Male Aging Study; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MrOS, Osteoporotic Fractures in Men Study; RCT, randomised controlled trial; SHBG, sex hormone-binding globulin; T, testosterone.

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1. Introduction

Demographic changes will result in an increasing proportion of older adults in countries around the world [1]. Ageing is accompanied by mortality, and also by increasing risk of frailty and disability [2]. Therefore, a priority for both biomedical researchers and health care professions is to identify modifiable risk factors for ill-health during ageing in order to develop novel interventions to preserve health in the increasing population of older adults. Male ageing is accompanied by characteristic alterations in circulating hormones, raising the question whether these changes represent potential modifiable risk factors for ill-health [3]. Testosterone (T), the primary male sex hormone or androgen, is produced by the testes in response to pituitary secretion of luteinising hormone (LH). In the circulation, T binds to sex hormone-binding globulin (SHBG) and with lesser avidity to albumin, with a small fraction unbound or free [4]. Circulating levels of T decline as men grow older [5,6]. While obesity and ill-health contribute to lower T levels [7,8], age remains independently associated with lower T levels in older men [9]. SHBG levels increase with age, therefore the decline in free T levels is steeper than that of total T [6,10]. The significance of free T (or the combination of free and albumin-bound T, referred to as "bioavailable T") and the contribution of the T metabolites dihydrotestosterone (DHT) and estradiol (E2) to modulate health outcomes in older men are debated [11]. Diagnostic testing for androgen status is typically based on measurement of total T, as free T is difficult to assay and it is commonly calculated from measured total T and SHBG [12]. There are limitations of measuring total T via automated immunoassays and mass spectrometry is more accurate for assessment of total T and also DHT and E2 [13]. This review will consider the associations of sex hormones with health outcomes encompassing cognitive impairment, dementia and mood disorders including depression in ageing men.

2. Testosterone, cognition and dementia: observational studies

2.1. Cross-sectional studies with cognitive outcomes

Several observational studies have documented associations of low circulating T with poorer performance in measures of cognitive function in middle-aged and older men. The Rancho Bernardo Study reported an analysis of 547 community-dwelling men aged 55–89 years in which total or bioavailable E2 correlated inversely with cognitive function as assessed using the Mini-Mental State Examination (MMSE), while bioavailable T correlated positively with memory and concentration [14]. Non-linear associations were reported for other cognitive tests, raising the prospect of an optimal hormone concentration. A limitation of that study was that cognitive testing was performed several years after the hormone assays. In a cross-sectional study from Pittsburgh of 371 men aged 50 years and older, those with higher bioavailable T had better scores on three tests of cognitive function including the MMSE [15]. In that study total E2 was inversely associated with cognitive test scores. By contrast a cross-sectional analysis of 981 men aged 48–80 years from the Massachusetts Male Aging Study (MMAS) found no association between total or free T and various cognitive measures [16]. Another cross-sectional analysis of 450 men aged 35–80 years suggested that men with lower free T performed better on spatial visualisation tasks compared to men with high free T levels [17]. However other studies support the link between higher T and better cognition in ageing men. A Netherlands study of 400 men aged 40–80 years reported a curvilinear association between total or bioavailable T with processing capacity and speed [18]. In that study the best scores for processing capacity and speed were found in men with total of bioavailable T in the 3rd and 4th quintiles of values. A Swedish study of 1107 men aged 35–90 years reported that higher free T levels were associated with visuospatial ability and memory [19]. The Western Australian Health In Men Study (HIMS) reported a cross-sectional analysis of 2932 men aged 70–89 years in which free T $\geq$210 pmol/L (20th centile) was associated with reduced likelihood of poor cognitive performance on the standardised MMSE [20]. A potential limitation of these studies was the measurement of T and where available E2 using immunoassays instead of mass spectrometry. Analyses were adjusted for age and education, and in some studies other covariates including alcohol, depression, other medical comorbidities and body mass index [14–20]. Thus while the published data has limitations, on balance these studies support associations of optimal T and to a limited extent lower E2 with better cognitive performance in middle-aged and older men.

2.2. Longitudinal studies and studies with the outcome of dementia

Of note, the above studies did not examine the outcome of dementia, and like any cross-sectional study cannot infer the direction of causality. In a UK study, men with Alzheimer's dementia (AD, $n = 112$) had higher LH and a lower ratio of total T:SHBG compared with aged-matched controls ($n = 98$) [21]. Post-mortem studies have also shown brain levels of T to be lower in cases of AD and mild neuropathology compared with neuropathologically normal men in the age range of 60–79, but not $\geq$80 years [22]. It is possible that T interacts with other risk factors for AD. For example, a study of 45 healthy men over 55 years of age found an interaction between free T and APOE $\varepsilon 4$ such that higher free T levels were associated with better general cognition in non-$\varepsilon 4$ carriers but with lower scores on tests of executive function, working memory and attention in $\varepsilon 4$ carriers [23]. Longitudinal studies have examined the association of baseline sex hormone levels with the risk of developing dementia. In the Baltimore Longitudinal Study of Aging, 407 men aged 50–91 years at baseline were followed for an average of 10 years [24]. A higher ratio of total T:SHBG predicted reduced rates of longitudinal decline in visual memory. In a separate analysis of 574 men from this cohort aged 32–87 years at baseline followed for a mean of 19.1 years, a higher ratio of total T:SHBG was associated with decreased risk of AD [25]. Of note, a longitudinal analysis of 2974 men aged 71–93 years from the Honolulu-Asia Aging Study followed over an average of 6 years showed that bioavailable T was not