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Hormones and health outcomes in aging men

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ABSTRACT

Increasing age is a predictor of ill-health and mortality related to cardiovascular disease and to frailty, a syndrome characterized by deterioration of multiple organ systems leading to loss of physiological reserve, diminished capacity to cope with stressors, and increased risk of disability and death. As men grow older, their levels of testosterone decline while the prevalence of ill-health increases. Observational studies have linked lower testosterone levels with cardiovascular disease and mortality in middle-aged and older men. More recently, lower testosterone has been shown to predict reduced sexual activity and frailty in aging men. Additional studies are needed to determine whether lower testosterone is a biomarker or a potentially treatable risk factor for poorer health outcomes in older men. During aging, the response of the pituitary–thyroid axis alters to manifest higher thyrotropin levels. The presences of subclinical hypo- and hyper-thyroidism predict adverse cardiovascular outcomes. Newer results indicate that in euthyroid older men, differences in free thyroxine levels within the normal range predict specific health outcomes including frailty. Clarification of the roles of endogenous testosterone and thyroxine in the genesis of ill-health during male aging offers the prospect of future intervention to preserve health and well-being in this growing population.

1. Introduction

Unprecedented demographic change will result in increasing aging of populations across developed and developing nations. It is estimated that 21% of the world population will be aged 60 years or more by 2050 (United Nations, 2001). Age is a major, irreversible risk factor for cardiovascular disease (CVD) and CVD-related mortality (Berry et al., 2012). Even if interventions at the levels of public health and clinical care succeed in reducing the rate of CVD mortality (Ford and Capewell, 2011), the increasing burden of CVD-related morbidity will consume greater proportions of limited health care resources (Roger et al., 2011). Additionally, age is closely associated with an increasing prevalence of frailty, a syndrome characterized by deterioration of multiple organ systems leading to loss of physiological reserve, diminished capacity to cope with stressors, and increased risk of disability and death (Fried et al., 2001; Ahmed et al., 2007). Therefore the identification of reversible risk factors for CVD and frailty in the elderly would represent an important advance in understanding and potentially reducing the burden of ill-health associated with aging.

Testosterone (T) is the primary male sex hormone or androgen which regulates virilization and body composition in men (Bhasin, 2008). Testicular secretion of T occurs in response to pituitary secretion of luteinizing hormone (LH), itself stimulated by pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus. T is present in the circulation bound to sex hormone-binding globulin or albumin, with only 0.5–3% unbound or free (Bhasin, 2008). T is aromatized into estradiol (E2), and in men some of the actions of T are mediated via E2 for instance in bone (Khosla et al., 2002; Gennari et al., 2004). Circulating levels of total T decline as men grow older, and this change approximates to a 1% decrease per year of increased age (Harman et al., 2001; Feldman et al., 2002; Liu et al., 2007). Men with low T levels can exhibit either increased LH (primary gonadal failure) or inappropriately normal LH (secondary hypogonadism). In the absence of proven pathological disruption of the hypothalamo–pituitary–gonadal axis, the latter category can be difficult to distinguish from results seen in aging men (Bhasin, 2008). There is intense interest in whether this age-associated change in the male androgenic environment represents a causal factor contributing to the increased burden of ill-health in older men (Yeap, 2009, 2010).

By contrast, the thyroid axis manifests a more subtle age-associated evolution. Pituitary secretion of thyrotropin (thyroid stimulating

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; E2, estradiol; FT_4, free thyroxine; GnRH, gonadotropin-releasing hormone; HR, hazard ratio; HIMS, Health In Men Study; IHD, ischemic heart disease; LH, luteinizing hormone; MI, myocardial infarction; MrOS, Osteoporotic Fractures in Men Study; T, testosterone; T3, triiodothyronine; TOM, Testosterone in Older Men with Mobility Limitations Trial; TSH, thyrotropin, thyroid stimulating hormone.

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hormone, TSH) stimulates production of free thyroxine (FT_4) and triiodothyronine (T_3) from the thyroid (Larsen et al., 2008). With aging, serum levels of TSH rise, while levels of FT_4 generally remain stable (Surks and Boucai, 2010; Bremner et al., 2012). There is increasing interest in potential adverse consequences of "subclinical" over- or under-activity of the thyroid axis, and more recently in whether differences in thyroid hormone levels within the normal range might influence health outcomes during aging.

2. Testosterone and cardiovascular events

Several observational studies have reported on the relationship between baseline sex hormone levels and the incidence of CVD events. In the Tromso study, total T level was not associated with first-ever myocardial infarction (MI) (Vikan et al., 2009). In the Caerphilly Study, total T was not associated with incident ischemic heart disease (IHD), rather the ratio of cortisol:T predicted IHD events (Smith et al., 2005). Higher total E2, not T, was associated with lower risk for CVD events in the Framingham study (Arnlov et al., 2006). Paradoxically, higher total E2, not T, predicted increased risk of stroke in men from the Honolulu-Asia Aging Study (Abbott et al., 2007). By contrast, the Western Australian Health In Men Study (HIMS) provided evidence that lower total or free T levels were independent predictors of incident stroke or transient ischemic attack in a large cohort of 3443 men aged ≥70 years (Yeap et al., 2009). In HIMS, men with higher baseline total or free T had reduced risk of IHD events, after adjustment for age and waist:hip ratio but not after adjusting for prevalent IHD or other cardiovascular risk factors; while higher LH was independently associated with increased incidence of IHD (Hyde et al., 2011). In the Osteoporotic Fractures in Men (MrOS) Sweden study involving 2416 men aged 69–81 years, higher total T levels predicted reduced incidence of CVD events after adjusting for known cardiovascular risk factors (Ohlsson et al., 2011). Therefore, while the data are not wholly consistent, evidence is available from large epidemiological studies relating lower T (or higher LH) levels with the incidence of CVD-related events in middle-aged and older men.

3. Testosterone and mortality

Numerous studies have examined the association of T with the outcome of all-cause or CVD-related mortality (for reviews see: Yeap, 2010; Araujo et al., 2011). The meta-analysis by Araujo et al. (2011) included 12 studies of which 11 involving 16,184 men examined the outcome of all-cause mortality, and 7 with 11,831 men CVD-related mortality. Low endogenous T levels were associated with increased risk of all-cause mortality (hazard ratio HR = 1.35, 95% confidence interval CI = 1.13–1.62); the association with CVD mortality not reaching statistical significance (HR = 1.25, 95% CI = 0.97–1.60). However, heterogeneity between studies raised the prospect that low T levels might reflect reduced general health. Since the publication of that meta-analysis, HIMS reported from their cohort of 3637 men aged 70–88 years that lower free T levels or higher LH predicted all-cause and CVD mortality (Hyde et al., 2012). Therefore, disruption of the pituitary–gonadal axis predicts mortality and deaths from CVD, but causality and the feasibility of intervention are not yet confirmed.

4. Testosterone and sexual activity

Recognized symptoms of androgen deficiency include lack of energy, lack of motivation and reduced libido (Kelleher et al., 2004; Bhasin et al., 2010; Wu et al., 2010). An important issue in the context of healthy aging is whether lower T, reflecting its association with lower libido, translates into reduced sexual activity in older men. In a follow-up of the HIMS cohort, 3274 men by then aged 75–95 years were surveyed using a questionnaire which included items on sexual activity (Hyde et al., 2010b). Sex was considered important by 48.8% of 2783 men who provided data on sexual activity. 30.8% had at least one sexual encounter in the past 12 months, defined as any mutually voluntary activity with another person that involves sexual contact, whether or not intercourse or orgasm occurred. Of these sexually active older men, 56.5% were satisfied with the frequency of sex, while 43.0% would have preferred sex more frequently (Hyde et al., 2010b). Increasing age, partner's lack of interest, partner's physical limitations, osteoporosis, prostate cancer, diabetes, anti-depressant use, and beta-blocker use predicted reduced sexual activity. Living with a partner, non-English speaking background and higher T levels were associated with sexual activity. Thus many older men considered sexual activity important and desirable, and social, physical, medical and hormonal factors are relevant to this desire (Yeap, 2011).

5. Testosterone and frailty

While frailty as a syndrome is familiar to physicians and researchers in the aged care environment, standardized operational definitions of frailty are more difficult to achieve (Van Kan et al., 2008; Rodriguez-Manas et al., 2012). The Fried criteria utilize the presence of three or more of five components: unintentional weight loss, exhaustion, poor grip strength, slow walking speed, or low physical activity (Fried et al., 2001). The FRAIL scale has been proposed as an alternative tool for screening for frailty (Van Kan et al., 2008). This utilizes five elements of fatigue, resistance, ambulation limitation, illnesses, and loss of weight, with frailty represented by the presence of three or more of these elements. Central to both these definitions is the presence of sarcopenia, or loss of lean muscle mass, closely associated with decreased muscle function which is a key factor in the genesis of frailty (Cooper et al., 2012).

T is an anabolic hormone which promotes accumulation of muscle mass (Page et al., 2005; Bhasin et al., 2005). Therefore, there is considerable interest in whether lower T levels in aging men predispose to frailty. A positive association of T with physical performance has been reported up to a threshold of total T of 15.6 nmol/L (O'Donnell et al., 2006), lower free T levels are associated with mobility limitation (Krasnoff et al., 2010) and men with higher baseline total T levels experience reduced loss of lean mass (LeBlanc et al., 2011). In HIMS, lower free T was associated with frailty both at baseline and at follow-up (Hyde et al., 2010a). In the Concord Health and Ageing in Men Project (CHAMP), lower total and free T were associated with frailty, and a decrease in total or free T predicted progression to or increase in severity of frailty in older men (Travison et al., 2011). Therefore, observational data support a relationship between lower T levels and increased risk of frailty in older men.

6. Testosterone trials in older men

There have been no randomized controlled clinical trials of T with the endpoints of CVD events or mortality (Kaufman and Vermeulen, 2005; Cunningham and Toma, 2011), as these would pose considerable logistical difficulties due to the large numbers of men and extended duration of treatment required to accumulate sufficient outcome events. Previous reviews or meta-analysis of existing T trials generally have not shown a signal for excess CVD events (Kaufman and Vermeulen, 2005; Haddad et al., 2007). In a trial of transdermal T in 60 men aged ≥55 years with total T <15 nmol/L, T therapy increased sexual desire (Allan et al., 2008). A meta-analysis of 17 randomized placebo-controlled trials including 656 men with average total T at baseline <12 nmol/L found that T treatment moderately improved nocturnal erections, sexual thoughts and motivation, frequency of successful intercourse and overall sexual satisfaction (Isidori et al., 2005b). Randomized clinical trials in middle-aged and older men have reported reduced fat and increased lean mass resulting from T therapy (Isidori et al., 2005a). Transdermal T (50 mg/d) in 274

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