

ORIGINAL ARTICLE

Hormone replacement therapy and longevity

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Keywords

Ageing—hormones—longevity—oestrogen therapy—testosterone therapy

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Accepted: March 4, 2015

doi: 10.1111/and.12419

Summary

To assess whether hormone replacement therapy influences longevity, an analysis was made of published life tables allowing for the calculation of the relative benefit of hormone replacement therapy on longevity in men with late onset hypogonadism and in post-menopausal women. It was found that testosterone replacement therapy of men suffering from late onset hypogonadism increased survival rate by 9–10% in 5 years, similar to that of eugonadal, non-LOH men with normal endogenous testosterone secretion. Oestrogen replacement therapy resulted in increased survival by 2.6% in 5 years. It is concluded that hormone replacement therapy increases longevity.

Introduction

Physiological male ageing implies progressive decrease in endogenous testosterone secretion with blunting of the day–night variation (Comhaire, 2000; Mahmoud & Comhaire, 2006). The overall exposure of the target cells decreases, which some authors suggest to protect against cerebrovascular accidents (Quillinan *et al.*, 2014). However, it is well established that neither testosterone replacement therapy in hypogonadal men, nor oestrogen-only replacement therapy in post-menopausal women (Comhaire & Depypere, 2015) increase the overall risk of cardiovascular disease (Baillargeon *et al.*, 2014), prostate cancer (Haider *et al.*, 2015) or breast cancer (Anderson *et al.*, 2012).

In fact, there is strong evidence that an increased ratio of oestradiol over testosterone is associated with a higher risk of vascular disease, both cerebrovascular (Gong *et al.*, 2013) and cardiovascular. In men, the oestradiol over testosterone ratio in blood is inversely correlated with the testosterone concentration. This is explained by the fact that there are two major sources of oestradiol, namely the metabolism of dehydroepiandrosterone (DHEA) secreted by the adrenal cortex (Artl *et al.*, 1999), and the aromatisation of testosterone produced by and in the testicular Leydig cells. Whereas the latter decreases in parallel with the secretion of testosterone, oestradiol originating from the metabolism of DHEA does not decrease, maintaining a substantial oestradiol concentration in blood (estimated by deduction from the Lineweaver–Burk plot at approximately 12–15 pg ml⁻¹). This

causes a relatively high oestradiol over testosterone ratio at low testosterone concentrations. Similarly, the high oestradiol over testosterone ratio induced by pharmaceutical interventions enhances the prevalence of cardiovascular pathology (Zuber, 2015). This occurs in case of androgen depletion therapy (Abrahamsson *et al.*, 2005; Martin-Merino *et al.*, 2011) or oestrogen treatment of patients with prostate cancer (Cox & Crawford, 1995), and in oestrogen supplementation of male-to-female transsexuals (Lioudaki *et al.*, 2010; Gooren *et al.*, 2014).

In a rather large, probably increasing proportion of the ageing male population's testosterone production decreases excessively causing the syndrome described as late onset hypogonadism (LOH, Wu *et al.*, 2010) associated with obesity, the metabolic syndrome (Ng Tang Fui *et al.*, 2013) and, to a lesser degree, type 2 diabetes. Men suffering from LOH were found to have a shorter life time and significantly higher mortality than eugonadal men (Saad & Gooren, 2014), even after adjustment for age, BMI, current smoking, diabetes (Muraleedharan *et al.*, 2013) and poor general health (Pye *et al.*, 2014; Zarotsky *et al.*, 2014).

Testosterone replacement therapy (TRT) has been recommended for patients with LOH, although some authors warn against its alleged misuse (Handelsman, 2013; Huhtaniemi, 2014). Testosterone replacement therapy corrects the estradiol over testosterone ratio, and there is increasing evidence that TRT has a protective effect against age-related diseases, but little is known about its influence on longevity.

If an adequate testosterone concentration would, indeed, reduce mortality, the question to be answered is

whether there is a difference between the effect of endogenously secreted compared with exogenously applied testosterone on longevity.

At the other hand, long-term oestrogen replacement therapy was found to reduce mortality of post-menopausal women (Ettinger *et al.*, 1996; Paganini-Hill *et al.*, 2006), but little is known about its possible life-extended effect on the long-term.

Materials and methods

Based on the graphic presentations of life tables (Kaplan–Meyer survival curves) published in three papers (Malkin *et al.*, 2010; Anderson *et al.*, 2012; Shores *et al.*, 2012), I have calculated the ratio of survival in the positive cases divided by that in control cases. The positive cases were the following cohorts: cohort 1: men with coronary heart disease and normal ‘endogenous’ bio-testosterone concentration of 2.6 nmol l^{-1} (74.9 ng dl^{-1}), or total testosterone concentration of 8.1 nmol l^{-1} (233 ng dl^{-1}) or more ($n = 736$) (Malkin *et al.*, 2010), cohort 2: LOH patients treated with testosterone injections ($n = 301$) (Shores *et al.*, 2012) and cohort 3: post-menopausal women who had undergone hysterectomy and were treated with oestrogen-only replacement ($n = 5,310$) (Anderson *et al.*, 2012). The controls were, respectively, cohort 1: men with low bio-testosterone concentration less than 2.6 nmol l^{-1} ($n = 194$), cohort 2: LOH patients not receiving TRT ($n = 301$) and cohort 3: post-menopausal women not using oestrogen replacement therapy ($n = 5,429$). These ratios were plotted against the duration of follow-up.

Results

The graph in Fig. 1 shows the ratio of the positive cases divided by the controls per cohort in relation to the time of follow-up. There is no difference between the curve of the ratios of cohort 1, men with normal versus low bio-testosterone, and the curve of cohort 2: treated versus untreated LOH patients. In both cohorts, the quotient is between 109 and 110% after 5 years in favour of the positive cases. The curve of cohort 3: oestrogen-treated versus untreated post-menopausal women is situated at a lower level, with 2.6% benefit in favour of the treated cases after 5 years.

Discussion

There is controversy regarding hormone replacement therapy in ageing men and women and its impact on the quality of life and survival. Although the general trend of recent publications is in favour of hormone replacement, it is not clear whether exogenous testosterone administration

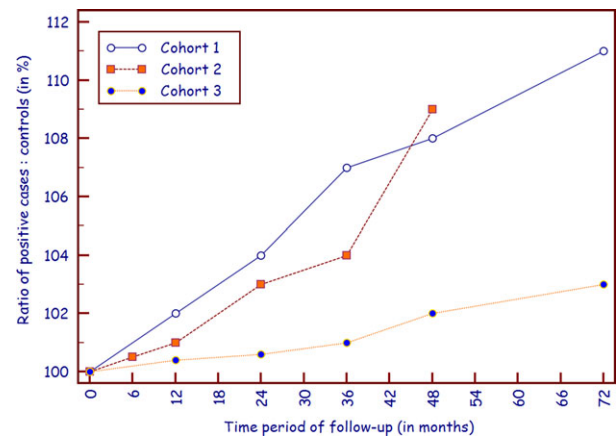


Fig. 1 The ratio (in %, on the vertical axis) of survival in positive cases divided by survival in controls is plotted against the time period of follow-up (in months, on the horizontal axis). The curves represent the results of the comparison of cohort 1: eugonadal men with endogenous bio(free)-testosterone concentration higher or lower than 2.6 nmol l^{-1} (free T male), of cohort 2: LOH patients either or not treated with testosterone replacement (HRT male), and of cohort 3: post-menopausal women either or not taking oestrogen replacement therapy (HRT female).

to LOH patients influences longevity similar to that observed in eugonadal, non-LOH men with ‘normal-for-age’ endogenous testosterone production. The former more commonly present obesity, the metabolic syndrome or diabetes, which by themselves may shorten life expectancy.

The simple mathematical approach taken in the present study may be subject to many critical objections, as it is based on a small number of publications including different types of cases, although the total number of observations is high ($n = 12\,271$). The findings suggest that replacement therapy with exogenous testosterone of patients with LOH extends survival to the same degree as that of eugonadal men with normal endogenous testosterone, with a gain of 9–10% after 5 years.

As far as oestrogen replacement therapy of post-menopausal women is concerned, our finding of increased survival by 0.52% person-years confirms the observation published by Paganini-Hill *et al.* (2006) reporting a reduced mortality rate between 0.36% and 0.61% person-years in ever-users and long-term users, respectively, compared with never-users.

Complementary prospective controlled trials of longer duration are warranted to confirm these findings.

Conclusion

The remarkable agreement between the curves of relative gain of survival in eugonadal men with adequate endoge-

nous testosterone production and in LOH patients treated with exogenous testosterone seems relevant. Together with the results in post-menopausal women, our findings lend support to the concept that low hormone levels, on their own, reduce life expectancy of both men and women and that hormone replacement therapy can extend longevity. In this regard, testosterone replacement in men with hypogonadism appears to be more efficient than oestrogen replacement in post-menopausal women.

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