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Brief Report:

Sex hormones and cause-specific mortality in the male veterans: The Vietnam Experience Study

Short title: Sex hormones and mortality

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Abstract

Background: Testosterone levels have been linked to life expectancy in men, less is known about the sex hormones follicular stimulating hormone and luteinising hormone.

Aim: To examine the association of testosterone, follicular stimulating hormone, luteinising hormone with mortality.

Design: Prospective cohort analysis.

Methods: Participants were 4255 Vietnam-era US army veterans with a mean age of 38.3 years. From military service files, telephone interviews, and a medical examination, socio-demographic, and health data were collected. Contemporary morning fasted hormone concentrations were determined. All-cause, cardiovascular, cancer, external and 'other' cause mortality was ascertained over the subsequent 15 years. Hazard ratios were calculated, first with adjustment for age and then, additionally, for a range of confounders.

Results: Individuals within the highest tertiles of FSH and LH levels were at increased risk of all-cause mortality following adjustment for a range of risk factors. However, with mutual adjustment, neither FSH nor LH significantly predicted mortality. Testosterone levels did not show an association with all-cause mortality, and none of the hormones were significantly associated with CVD, cancer, 'other' or external-cause mortality in fully-adjusted models.

Conclusions: Greater FSH and LH levels are associated with all-cause mortality, but not independently of one another.

Introduction

Testosterone levels in men decline incrementally from middle age onwards, resulting in low levels (<5ng/ml) in approximately 20% of men aged 50 years, and 50% among those aged 80 years [1]. Recently evidence suggests that low testosterone levels among men are associated with elevated mortality, independent of age and lifestyle factors [2-5]. These effects appear to be independent of major risk factors for premature mortality [6, 7], and are also seen for specific causes of mortality such as cardiovascular disease and cancer. However, given the associations between low testosterone and coronary artery disease [8] and other cardiovascular risk factors [9], it is not surprising that among men with existing cardiovascular disease [10], or recent acute myocardial infarction [11], low testosterone was related to cardiovascular disease mortality as well as all-cause mortality. In the Caerphilly study [12] and the Massachusetts Male Aging Study [13], total testosterone level was unrelated to mortality. One of these null studies has been criticised for not including key confounding variables such as medical diagnoses, depression, and alcohol consumption, known to affect testosterone levels [14]. Further, few studies have examined the predictive ability of testosterone for cancer, and other medical cause mortality. There is also a very modest literature exploring the role of other gonadotrophic hormones such as follicle stimulating hormone (FSH), and luteinizing hormone (LH) as risk factors for mortality. In the present analyses we address these issues. Testosterone, FSH, and LH levels were examined in relation to all-cause, cardiovascular, cancer, external, and other cause mortality among a large sample of male US veterans from the Vietnam Experience Study that is well characterised for covariates.

Participants and Methods

Participants (N = 4256) were identified from data gathered as part of the Vietnam Experience Study, details of eligibility criteria and sampling elsewhere [15-17], representing 23.3% of persons originally enrolled in the study based on the recruitment of a random sample of surviving men. Differences between persons these and the full sample were very small: men in the analytical sample had higher IQ

test scores (means of 101.3 versus 100.4, $p = .001$) and a greater proportion had service experience in Vietnam (55% versus 51%, $p < .001$). We believe that these marginal differences reached statistical significance due to the large sample size.

Place of service, military rank, ethnicity, and cognitive ability scores from the Army General Technical Test (hereafter referred to as "IQ") was extracted from the military archives. In 1985, participants were invited to participate in a telephone interview; educational grade achieved at school and household income in midlife were determined as measures of socio-economic status. Alcohol consumption, cigarette smoking and marital status were ascertained using standard questions. Participants were also asked whether or not they had a range of somatic physician-diagnosed health problems which included hypertension, cancer, diabetes and coronary heart disease [18, 19]. In 1986, a random sample of telephone interview respondents was invited to attend a three day medical examination. The mean age at medical examination was 38.3 years (range: 31.1 to 49.0). From fasted blood samples, cholesterol and serum glucose levels were determined [18, 19]. Resting blood pressure and height and weight were measured using standard protocols. Psychological morbidity (Generalised Anxiety Disorder, Major Depressive Disorder, or Post-traumatic Stress Disorder (GAD, MDD, PTSD) in the previous 12 months) according to the Diagnostic and Statistical Manual of Mental Disorders (version III) criteria was assessed using the Diagnostic Interview Schedule (version 3A) [20, 21]. Serum FSH, LH, and testosterone were assayed using a double antibody radioimmunoassay system (Leeco Diagnostics, Inc., Southfield, MI). Blind repeat test correlations exceeded 0.98. Bench controls yielded intra and inter-assay coefficients of variation < 10%.

The vital status of men between army discharge and December 31st 1983 (the date the cohort was established) was ascertained by cross-checking against a variety of mortality databases (details elsewhere [22]) until 31st December 2000, with a mean follow-up time of 14.6 (SD = 1.76) years). Cause of death was classified using the International Classification of Diseases (ICD) [23] into the following categories: major

CVD , cancer, and external causes (details elsewhere [24]). 'Other' causes of death were calculated as all-cause mortality minus the other classifications, and consisted of infectious diseases, liver diseases/failure, kidney diseases/failure, and respiratory diseases. The most frequent causes of death in this category were from infection, including infection with Human Immunodeficiency Virus (HIV), and from liver disease.

For analysis, sex hormone levels were split into tertiles and Cox's proportional hazards regression was used to examine the relationships between tertiles of each hormone, and each mortality outcome, adjusting for age and the covariates listed above. These covariates were chosen *a priori* as they have all been associated with mortality in this dataset [25, 26] and others [27]. Significance was set at $p \leq 0.05$.

Results

The sample mean (SD) testosterone, FSH, and LH levels were 679.5 (234.81) ng/dL, 7.9 (6.44), and 14.2 (5.92) IU/L, respectively. The mean (SD) hormone levels for each tertile of the sample are shown in Table 1 along with the baseline characteristics of those in each tertile. Testosterone and FSH levels were not correlated but testosterone was positively correlated with LH, r = .12, and FSH and LH levels were positively correlated, r = .60.

[Insert Table 1 about here]

During the 15 years of follow-up there were 236 deaths. Higher mortality was associated with not being married, being non-white, having lower IQ, lower household income in midlife, higher blood pressure and blood glucose level, smoking; higher intake of alcohol per week; and higher prevalence of physician-diagnosed physical illness at examination. Those in the highest tertile of FSH had a significantly higher likelihood of mortality in comparison to those in the lowest tertile, HR = 1.47, 95%CI 1.04-2.09. Individuals in the highest tertile of LH also had a higher risk of all-cause mortality, HR = 1.44, 95%CI 1.02-2.03. Testosterone level was not associated with all-cause mortality in age-adjusted analyses or

other models. Testosterone, FSH, and LH were not associated with mortality from CVD, cancer, external causes, or other causes.

The significant analyses for all-cause mortality predicted by FSH and by LH were repeated removing those who had died in the first two years following the medical examination in order to take early sub-clinical morbidity into account. The results for FSH remained significant, HR = 1.46 (95%CI = 1.02 – 2.09), p = .04, such that those in the highest tertile were at greater mortality risk. However, the association for those in the highest tertile of LH was attenuated to a trend, HR = 1.40 (95%CI = 0.99 – 2.00), p = .06. When significant associations for all-cause mortality were repeated entering both FSH and LH simultaneously, neither hormone predicted an increased risk of mortality. This may be explained by the highly significant correlation between FSH and LH concentrations.

Discussion

FSH and LH, but not testosterone, concentration were significantly associated with all-cause mortality. Those in the highest tertiles of FSH or LH were more likely to die during follow-up, after adjustment for a comprehensive range of potential confounding variables, and after removing those with early mortality, although it should be noted that the association for LH was attenuated to a trend, probably due to lowered power. However, these effects were not independent of one another, and FSH and LH concentrations were highly correlated, suggesting that these hormones can be used interchangeably to predict mortality. This probably reflects that alterations in secretion of FSH are paralleled by alterations in LH and vice versa in many conditions including ageing [28].

What might be the mechanism by which higher levels of FSH and LH were related to increased all-cause mortality? Low levels of such hormones may reflect dysregulation in response to stress or the presence of critical illness [29]. However, higher levels have been associated with ageing [28] sperm motility and

concentration [30]. Thus, higher levels of these hormones may be compensating for a deficiency in the ability of the gonads to produce testosterone associated with both age and decreased fertility. Alternatively, higher levels of LH and FSH may reflect underlying undiagnosed diseases, for example, arthritis, which may later contribute to risk of other morbidities and mortality. Percentage change in FSH and LH has been shown to correlate positively with changes in proinflammatory cytokines relevant to arthritis activation [31]. Similarly, increases in FSH and LH have been shown to parallel bouts of acute illness in the elderly [32].

That testosterone level did not predict all-cause mortality is surprising, given the evidence from previous studies showing a negative association [2-7]. However, other studies have also failed to show an association [12, 13]. Some of which have been criticised for a lack of control for potential confounding variables such as medical diagnoses, alcohol consumption, and depression [14], however these variables were adjusted for in the present analyses. A potential reason for the lack of association might be the young age of the population studied and thus younger age at follow-up, resulting in fewer deaths overall. In all of the previous studies finding an association, the participants were middle-aged and elderly, and in those not finding a relationship, the mean ages were younger by approximately two decades [33], whereas in the present sample, the mean age was even younger at 38.3 years. Testosterone levels were also much higher (679.5 ng/dL), probably due to the age of the sample, than in previous studies finding an association where levels were less than 241ng/dL [2] and those which did not, such as the Massachusetts study were levels were less than 370ng/dL [13, 33]. It is possible that associations between testosterone and mortality do not emerge until later in life when testosterone levels are lower.

The lack of associations for other sub-types of mortality may reflect the low numbers within these categories, given the age of the sample, resulting in lower power to detect significant associations, particularly when adjusting for a large number of covariates. Support for this assertion can be found in

the non-significant hazard ratios which were of comparable size for both all-cause mortality and other types. The present sample was exclusively male, thus there is also the issue of generalisation, and it should be noted that the previous studies with null results for testosterone were also male samples [12, 13], although these studies had much smaller samples, reducing their power to detect effects.

In conclusion, the present analysis in Vietnam veterans showed that those in the highest tertile of FSH and LH levels, were at increased risk of all-cause mortality, independently of adjustment for a range of socio-economic, behavioural and health-related variables. However, these effects did not emerge independently of each other.

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Declaration of Interest: The authors have nothing to disclose.

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