Serum testosterone but not leptin predicts mortality in elderly men

SIR—In men ageing is associated with a gradual progressive decline of total serum testosterone concentration [1–5]. A substantial proportion of older men, ranging from 20% in 60 years old to 50% in 80 years old, have testosterone concentrations below the normal range of younger men [4]. Low testosterone associates with occurrence of various cardiovascular risk factors [6, 7], and most epidemiological studies suggest that association of testosterone with coronary artery disease is either favourable or neutral [8]. Some studies have suggested that leptin is also an independent predictor of cardiovascular morbidity and mortality [9–11], but this association has not been seen in all studies [12]. After adjustment for age, concentration of testosterone in serum is inversely correlated with intima-media thickness of the carotid artery, whereas no such association is seen between serum leptin and carotid artery thickness [12]. Thus, endogenous testosterone may have a protective role in the development of atherosclerosis in ageing men, but information on associations between testosterone and mortality or coronary heart disease is lacking.

We performed a longitudinal 10-year study to clarify the association of endogenous testosterone and leptin with all-cause mortality in ageing men. The results suggest an association between low endogenous testosterone concentration and mortality in elderly men.

Subjects and methods

During the years 1991–92, a survey investigating the health of elderly men in the city of Turku, Southwest Finland, was performed. All home-dwelling male residents at the specified age and living in the defined geographical area were offered the possibility to participate; 370 men (73%) responded. Testosterone measurements were available for 310 men. We then excluded subjects with diabetes mellitus (n = 23), subjects being unable to walk at least 500 m (n = 49) and those experiencing themselves either sick or very sick at the time of the investigation (n = 51). The age of the remaining 187 men was between 71 and 72 years at the time of inclusion in the study.

The subjects visited a local health centre for medical examination, had an oral glucose tolerance test done and after an overnight fast donated serum for further studies. A list of questions such as the use of alcohol (nil/less often than once a week/at least once a week), smoking habits (yes/has finished/no) and the drug use were also asked, and the Zung self-rating depression scale questionnaire [13] was completed. The diagnosis of cardiac insufficiency and coronary heart disease, if any, was based on clinical examination and medical records. The study was approved by the local Institutional Ethics Committee. For descriptive demographic and biochemical data of the participants, please see Appendix 1 in the supplementary data on the journal’s website (http://www.ageing.oupjournals.org).

The cohort was followed up for 10 years. Time and cause of death of deceased men were ascertained from the national
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Death Register kept by Statistics Finland, and the causes were categorised as cardiovascular and other. The register covers information on all death certificates of Finnish residents, and assures complete coverage. A unique national personal identification number assigned to every permanent resident of the country was used in the computerised record linkage.

The statistical calculations were performed with SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). The power analysis was performed with NCSS 2004 (Kaysville, UT, USA) software. A P-value <0.05 was considered as statistically significant. For details on laboratory and statistical methods, please see Appendix 2 in the supplementary data on the journal’s website (http://www.ageing.oupjournals.org).

Results

During the 10-year follow-up, 68 out of 187 men had died. The cause of death was cardiovascular in 27 cases.

The mean baseline serum testosterone concentration was ~14% higher (P<0.024) in men who were alive at the end of the follow-up period compared to the deceased men, whereas serum leptin did not differ between the groups (Table 1). There was no difference in serum testosterone and leptin concentrations between subjects with cardiovascular and other causes of death.

Table 1. The concentrations of testosterone and leptin in serum at inclusion according to the mortality during the 10-year follow-up

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Alive (n = 119)</th>
<th>Dead (n = 68)</th>
<th>F (1,185)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (mmol/l)</td>
<td>23.1 ± 9.2</td>
<td>20.2 ± 6.6</td>
<td>5.17</td>
<td>0.024</td>
</tr>
<tr>
<td>Leptin (µg/l)</td>
<td>7.99 ± 5.42</td>
<td>7.54 ± 4.74</td>
<td>0.32</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Means ± SD are given, n = 187.

The logistic regression analysis including information on cardiovascular diseases and potential confounding factors (Table 2) was performed among men with complete data (n = 152). Testosterone concentration at baseline was inversely associated with mortality (P = 0.021). A direct association existed between smoking and mortality (P = 0.0005), but not between leptin (P = 0.59) or any other factors with mortality. Similar findings were seen in the Cox regression analysis. In addition, the use of alcohol (P = 0.025) and self-rated depression value (P = 0.022) were inversely associated with the risk to die.

The adjusted odds ratio (OR) and hazard ratio (HR) (95% confidence interval) for testosterone to explain mortality and hazard to die were 0.93 (0.87–0.99) and 0.95 (0.91–1.00), respectively, indicating a favourable effect of endogenous testosterone on survival in elderly men. The corresponding OR and HR for leptin were 0.97 (0.87–1.08) and 0.97 (0.89–1.06), respectively, indicating that the effect of leptin was not statistically significant.

Discussion

We demonstrate for the first time that serum total testosterone concentration in elderly men is inversely associated with mortality. This association is independent

Table 2. Regression coefficients (and their standard errors) of the association of the variables with death (logistic regression analysis) and life expectancy (hazard to die, Cox regression analysis) over 10 years in aged men (n = 152: alive 100, dead 52)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Death Estimate</th>
<th>Standard error</th>
<th>Hazard to die Estimate</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (mmol/l)</td>
<td>-0.0729</td>
<td>0.0316</td>
<td>-0.0508</td>
<td>0.0240</td>
</tr>
<tr>
<td>Leptin (µg/l)</td>
<td>-0.0302</td>
<td>0.0555</td>
<td>-0.0301</td>
<td>0.0448</td>
</tr>
<tr>
<td>Coronary heart disease (no/yes)</td>
<td>0.2165</td>
<td>0.5776</td>
<td>0.2481</td>
<td>0.4446</td>
</tr>
<tr>
<td>Smoking (no/has finished/yes)</td>
<td>1.2552</td>
<td>0.3620</td>
<td>1.0760</td>
<td>0.2721</td>
</tr>
<tr>
<td>Cardiac insufficiency (no/yes)</td>
<td>0.3649</td>
<td>0.8317</td>
<td>0.5311</td>
<td>0.6019</td>
</tr>
<tr>
<td>Zung depression scale</td>
<td>-0.0422</td>
<td>0.0290</td>
<td>-0.0536</td>
<td>0.0234</td>
</tr>
<tr>
<td>Number of drugs in use</td>
<td>-0.2013</td>
<td>0.1403</td>
<td>-0.1563</td>
<td>0.1056</td>
</tr>
<tr>
<td>Use of alcohol (nil/less than once a week/at least once a week)</td>
<td>-0.6610</td>
<td>0.3458</td>
<td>-0.5712</td>
<td>0.2552</td>
</tr>
<tr>
<td>f-Cholesterol (mmol/l)</td>
<td>0.0797</td>
<td>0.2117</td>
<td>0.0464</td>
<td>0.1702</td>
</tr>
<tr>
<td>f-Triglycerides (mmol/l)</td>
<td>-0.2283</td>
<td>0.3761</td>
<td>-0.1794</td>
<td>0.3121</td>
</tr>
<tr>
<td>f-HDL-cholesterol (mmol/l)</td>
<td>0.3724</td>
<td>0.7004</td>
<td>0.5132</td>
<td>0.5288</td>
</tr>
<tr>
<td>Insulin 0 h (U/ml)</td>
<td>0.0189</td>
<td>0.0657</td>
<td>-0.0093</td>
<td>0.0513</td>
</tr>
<tr>
<td>Insulin 2 h (U/ml)</td>
<td>0.0002</td>
<td>0.0073</td>
<td>0.0025</td>
<td>0.0057</td>
</tr>
<tr>
<td>Glucose 0 h (mmol/l)</td>
<td>0.0138</td>
<td>0.3141</td>
<td>0.1604</td>
<td>0.2589</td>
</tr>
<tr>
<td>Glucose 2 h (mmol/l)</td>
<td>-0.0777</td>
<td>0.1338</td>
<td>-0.1132</td>
<td>0.1092</td>
</tr>
</tbody>
</table>

Statistically significant parameters are given in bold. Only men with complete information on the risk factors were included in the models. f, fasting. Insulin/glucose 0 h and 2 h denote insulin concentrations at times 0 h and 2 h, respectively, during OGGTT.
of several confounding factors. The magnitude of the associations is modest but statistically significant.

To reduce confounding by other factors potentially reducing survival, we excluded patients with frank diabetes, being frail or experiencing themselves as sick or being in institutionalised care. Our results therefore apply to home-dwelling men in rather good physical and mental condition.

Our results corroborate earlier findings from cross-sectional studies in a cohort followed for 10 years and agree with a recent study showing an inverse association between serum testosterone and severe aortic atherosclerosis and its progression in men [14].

The reasons of the favourable effects of testosterone may be mediated through reduced vascular risk. For example, testosterone influences lipoprotein patterns in a favourable way [15]. Other mechanisms may be important as well. Low testosterone concentration is associated with an increased risk for bone resorption and falls [16, 17], and with low-trauma hip fractures [18, 19]. In older men, low testosterone levels are found in subjects with depressed mood and reduced cognitive function [20, 21].

The adverse effects of smoking are well known [22], and therefore the association of smoking with risk to die was not surprising. Also, in the Cox regression model, the use of alcohol was associated with a beneficial outcome. This is in accordance with the J-shaped association of the use of alcohol and mortality reported earlier [23]. Apart from small number of subjects with high value in Zung depression scale, indicative for depressive mood, we could not find any obvious explanation for the inverse association of the scale with hazard to die.

Hypoleptinaemia has also been claimed to be an independent predictor of cardiovascular morbidity and mortality in several pathologic conditions [9–11], but results have been inconsistent [12]. Our results do not support the concept that leptin would be an independent predictor of mortality in elderly men.

In summary, we have demonstrated an independent inverse association between endogenous testosterone concentration in serum and mortality in 70-year-old non-diabetic men followed for 10 years. The results do not allow conclusions on causality. The association may be coincidental and reflect some underlying disease process. Use of exogenous testosterone in elderly men to reduce mortality cannot be recommended so far.

Key points
- An inverse association between serum testosterone at baseline and mortality was evident when elderly men were followed for 10 years.
- The association existed even after adjusting for confounding variables, including leptin.

Conflicts of interest
None

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Performance of the Goldberg Anxiety and Depression Scale in older women

SIR—The exact nature of the relationship between anxiety and depression in older people remains unclear, as evidence suggests that older adults are more likely than younger adults to manifest mixed anxiety and depression [1–4]. There is a frequent co-occurrence of anxiety and depression in older people in community-based studies, clinical settings and in institutions [5,6]. Data also suggest that the distinctive features of anxiety and depression become less pronounced with increasing age [7], and that the experience of anxiety and depression may in fact differ qualitatively with increasing age [8].

The Goldberg Anxiety and Depression Scale (GADS) is an 18-item self-report symptom inventory that was developed by Goldberg and colleagues from 36 items in the Psychiatric Assessment Schedule [9]. The GADS has been used in several studies of community-dwelling older adults [10]. McKinnon et al. (1994) [7] administered it to 832 older community-dwelling residents from Canberra, Australia (mean age = 76 years, SD = 4.9). Latent trait analyses demonstrated that the GADS items defined two correlated dimensions of anxiety and depression, with a third sleep disturbance factor also detected [7]. Christensen et al. (1999) [8] used structural equation modelling and found anxiety and depression to be highly correlated but distinct entities.


We aim to extend previous work with the GADS by exploring the relationship between anxiety and depression in a large-scale national population sample of older Australian women.

Methods

Participants

Participants were selected from the older cohort of The Australian Longitudinal Study on Women’s Health (ALSWH), which has been running since 1996. Characteristics of the participants have been described elsewhere [13]; details of attrition over time (in this age group mainly through death or frailty) have been given by Lee et al. (2005) [14]. This analysis is based on data from the third survey of the older cohort conducted in 2002 when the women were aged 75–80 years.

Measures

The GADS score is based on responses of ‘yes’ or ‘no’ to nine depression and nine anxiety items, asking how respondents feel: ‘Have you been a very nervous person?’ and ‘Have you felt calm and peaceful?’ The depression items are ‘Have