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ORIGINAL RESEARCH ARTICLE

Low testosterone concentrations and prediction of future heart failure in men and in women: evidence from the large FINRISK97 study

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Abstract

Aims The increased incidence of heart failure in men suggests that endogenous sex hormones might play a role in the development of heart failure, but epidemiological data remain sparse. Here, we evaluated the predictive value of low testosterone levels on future heart failure in the large population-based FINRISK97 study.

Methods and results Baseline serum testosterone concentrations were measured in 7855 subjects (3865 men and 3990 women) of the FINRISK97 study. During a median follow-up (FU) of 13.8 years, a total of 564 heart failure events were recorded. The age-adjusted baseline testosterone levels did not differ significantly between subjects developing incident heart failure during FU and those without incident events during FU (men: 16.6 vs. 17.1 nmol/L, $P = 0.75$; women: 1.15 vs. 1.17 nmol/L, $P = 0.32$). Relevant statistically significant correlations of testosterone levels were found with high-density lipoprotein cholesterol levels ($R = 0.22$; $P < 0.001$), body mass index ($R = -0.23$; $P < 0.001$), and waist-to-hip ratio ($R = -0.21$; $P < 0.001$) in men, while statistically significant correlations in women were negligible in effect size. In sex-stratified Cox regression analyses, taking age into account, a quite strong association between low testosterone and incident heart failure was found in men [hazard ratio (HR) 1.51 (95% confidence interval, CI: 1.09–2.10); $P = 0.020$ for lowest vs. highest quarter], but not in women [HR 0.70 (95% CI: 0.49–0.98); $P = 0.086$ for lowest vs. highest quarter]. Nevertheless, this association turned non-significant after full adjustment including body mass index and waist-to-hip ratio, and testosterone levels were no longer predictive for incident heart failure—neither in men [HR 0.99 (95% CI: 0.70–1.42); $P = 0.77$ for lowest vs. highest quarter] nor in women [HR 0.92 (95% CI: 0.64–1.33); $P = 0.99$ for lowest vs. highest quarter]. Accordingly, Kaplan–Meier analyses did not reveal significant association of testosterone levels with heart failure.

Conclusions Low levels of testosterone do not independently predict future heart failure.

Keywords Testosterone; Heart failure; Biomarker; Prognosis

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Introduction

While heart failure numbers in Europe are increasing, the incidence and prevalence remain lower in women than in men.[1] Men and women with heart failure also differ in disease distribution, preceding risk factors, and long-term prognosis.[1] This imbalance suggests that endogenous sex hormones might play a role in the development of heart failure, but epidemiological data remain sparse. Various studies have evaluated the relevance of circulating testosterone concentrations for cardiometabolic disease, and low testosterone concentrations have been associated with diabetes, atrial fibrillation, stroke, coronary heart disease, and mortality.[2–4] Evidence regarding the effect of

low testosterone levels on heart failure is limited. Multiple studies have linked testosterone deficiency with risk factors of heart failure, like hypertension, overweight and visceral obesity, and an activated inflammatory status.[5] Most of these studies suffer limitations like small sample size, limited follow-up, and incomplete statistical adjustment.[5] Nevertheless, just recently, a new report from the ARIC Study reported a weak, although statistically significant association between testosterone and incident heart failure in a general American community.[6] This borderline finding was only evident in overall analyses and needs to be replicated in further studies and populations.[6] Therefore, here, we evaluated the predictive value of low testosterone levels on future heart failure in the large European population-based FINRISK97 study.

Methods

In this study, all analyses and biomarker measurements were performed within the frame of the BiomarCaRE Consortium.[7]

Study population

This study is based on subjects of the FINRISK97 study aged 25–74 years drawn from the national Finnish population register in 1997. The study design has been published elsewhere.[8,9] In total, 11 500 individuals were invited and 8444 (73%) participated in the clinical examination. During the follow-up period of up to 15 years, the follow-up rate was 100% for the participants who continued living in Finland. Those who had permanently moved abroad (~0.5% of the participants prior to 31 December 2011) were lost to follow-up. All individuals enrolled in the study received a physical examination and a self-administered questionnaire, and a blood sample was drawn. For the present paper, participants with missing covariates and data, pregnant women, as well as individuals on testosterone supplementation therapy, and individuals with prevalent heart failure (n = 159, 1.9%) were excluded, and the analysis is based on 7855 individuals. The investigation conforms to the principles outlined in the *Declaration of Helsinki*.[10] The Ethics Committeev of the National Public Health Institute approved the study. All subjects gave written informed consent.

Outcome information

Outcome information on heart failure, as either primary disease or co-morbidity, was gathered from the National Hospital Discharge Register, the National Causes of Death Register, and the National Drug Reimbursement Register. The definition of the endpoints was according to MORGAM criteria, and the use of Finnish national healthcare registries for the identification of cardiovascular outcomes has been validated.[11]

Laboratory methods

Blood samples were stored under standardized conditions at −70°C. Routine laboratory parameters were measured at the Disease Risk Unit in the National Institute for Health and Welfare, Helsinki. Testosterone levels were measured using a chemiluminescent microparticle immunoassay (Abbott ARCHITECT 2nd Generation Testosterone; Abbott Diagnostics, USA) at the BiomarCaRE/MORGAM Laboratory, University Heart & Vascular Center, Hamburg, Germany. The assay range was 0.45–35 nmol/L, the intra assay coefficient of variation wa 3.57%, and the inter-assay coefficient of variation was 8.83%. Testosterone levels below or above the assay range were assigned as follows: for levels below 0.45 nmol/L, 0.45 nmol/L was used, and for levels reported to be >35.0 nmol/L, 35.0 nmol/L was used. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

Statistical methods

Multiple imputation was used for the management of missing values.[12] Baseline characteristics are presented as percentages for dichotomous variables and as means and standard deviations (SDs) for continuous variables. In case the distribution was skewed, median and lower/upper quartiles are reported. Age-adjusted Pearson correlation coefficients were calculated. Kaplan–Meier curves for heart failure were produced using categorized (by quartiles) testosterone concentrations. Cox regression models with age as the timescale were used, and each sex was considered separately because of the different shape of the testosterone distributions of men and women. Evaluation of the proportional hazards assumption and validity of Cox model results was tested and determined. Cox regression was performed with testosterone levels as a continuous and a categorized variable. Continuous testosterone levels were log transformed for women and left untransformed for men. Two different adjustments were used. Model 1 adjusted only for region of Finland (east and west), while Model 2 additionally adjusted for log-transformed total cholesterol, log-transformed high-density lipoprotein (HDL) cholesterol, log-transformed systolic blood pressure, known hypertension, known diabetes, smoking status, waist-to-hip ratio (WHR), body mass index (BMI), and time period of blood draw, because testosterone values undergo circadian rhythm.[13] R Version 3.2.2 (R Foundation for Statistical

Computing, Vienna, Austria) was used for all analyses. All tests were two tailed, and $P < 0.05$ was considered statistically significant.

Results

The baseline characteristics of the study participants are presented in *Table 1*. The mean age of the participants was 48.2 years for men and 46.9 years for women, and men had more cardiovascular risk factors than women. Circulating testosterone levels were higher in men, with a mean of 17.1 (SD 9.17) nmol/L in men and a median of 1.15 (SD 0.69) nmol/L in women ($P < 0.001$) [median values (lower/upper quartiles): 17.0 (12.8, 22.0) and 1.15 (0.87, 1.56)]. As further shown in *Table 1*, during a median follow-up of 13.8 years, a total of 319 incident heart failure cases (8.3%) were recorded in men and 245 cases in women (6.1%). Testosterone levels did not differ between cases and non-cases: 1.17 nmol/L in cases vs. 1.15 nmol/L in non-cases for men and 16.6 nmol/L in cases vs. 17.1 nmol/L in non-cases for women (data not shown; $P = 0.57$ in men and $P = 0.32$ in women).

Pearson correlation coefficients were calculated in order to assess the correlation of testosterone levels with clinical variables (*Table 2*). BMI, WHR, and HDL cholesterol were predictors of testosterone levels, although the effect was negligible. In detail, age-adjusted Pearson analyses revealed weak, however statistically significant correlations of testosterone levels with smoking, HDL cholesterol levels, systolic blood pressure, and relevant correlations with BMI ($R = -0.23$; $P < 0.001$) and WHR ($R = 0.21$; $P < 0.001$) in men and statistically significant, but clinically negligible correlations with estimated glomerular filtration rate, systolic blood pressure, and age in women.

Within the basic Model 1, sex-stratified Cox regression analyses, taking age into account, suggested a quite strong and statistically significant association between testosterone levels and future heart failure in men [hazard ratio (HR) 1.51 (95% confidence interval, CI: 1.09–2.10); $P = 0.020$ for lowest vs. highest quarter], but not in women [HR 0.70 (95% CI: 0.49–0.98); $P = 0.086$ for lowest vs. highest quarter] (*Table 3*). However, as further shown in *Table 3*, after multivariate adjustment, including BMI and WHR, the association weakened and Cox regression did not yield any significant association between testosterone levels and future heart failure in Model 2—neither in men [HR 0.99 (95% CI: 0.70–1.42); $P = 0.77$ for lowest vs. highest quarter] nor in women [HR 0.92 (95% CI: 0.62–1.33); $P = 0.99$ for lowest vs. highest quarter]. Accordingly, Kaplan–Meier analyses did not reveal significant association of testosterone levels with heart failure (*Figure 1*).

Discussion

In the last years, a wide set of blood-based cardiometabolic biomarkers have been evaluated for its predictive capacity in cardiovascular disease.[14–28] Within these candidates, especially testosterone has gained special interest, because testosterone supplementation therapy is widely used.[29] Previously endogenous testosterone levels have already been reported to be linked to behavioural habits—sexual behaviour, alcohol consumption, nutrition, physical exercise, and psychic and psychosomatic stress, while recent research

Table 2 Age-adjusted Pearson correlation coefficients of serum testosterone levels with clinical variables

	Men *R*; *P*-value	Women *R*; *P*-value
Age	0.01; 0.52	0.05; 0.007
Smoking	0.09; <0.001	−0.01; 0.65
Total cholesterol	<0.009; 0.93	−0.01; 0.58
HDL-C	0.22; <0.001	−0.03; 0.087
Systolic blood pressure	−0.05; 0.009	0.03; 0.046
eGFR	0.01; 0.63	−0.05; 0.004
BMI	−0.23; <0.001	0.03; 0.13
WHR	−0.21; <0.001	0.04; 0.053

BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; WHR, waist-to-hip ratio.

Table 1 Characteristics of study participants at baseline and events during FU

	Men *n* = 3865	Women *n* = 3990
Age (years) (SD)	48.2 (22.6)	46.9 (21.0)
BMI (kg/m^2) (SD)	26.5 (4.8)	25.5 (6.3)
Current smoker (%)	26.4	17.5
Diabetes (%)	5.5	4.7
Hypertension (%)	16.9	13.8
HDL-C (mmol/L) (SD)	1.23 (0.39)	1.51 (0.47)
Total cholesterol (mmol/L) (SD)	5.5 (1.4)	5.4 (1.4)
Systolic blood pressure (mmHg) (SD)	137 (26)	130 (27)
Testosterone (nmol/L) (SD)	17.07 (9.17)	1.15 (0.69)
(25th P, 75th P)	(12.82, 21.99)	(0.87, 1.56)
Incident heart failure events during FU (%)	319 (8.3)	245 (6.1)

BMI, body mass index; FU, follow-up; HDL-C, high-density lipoprotein cholesterol; P, percentile; SD, standard deviation.

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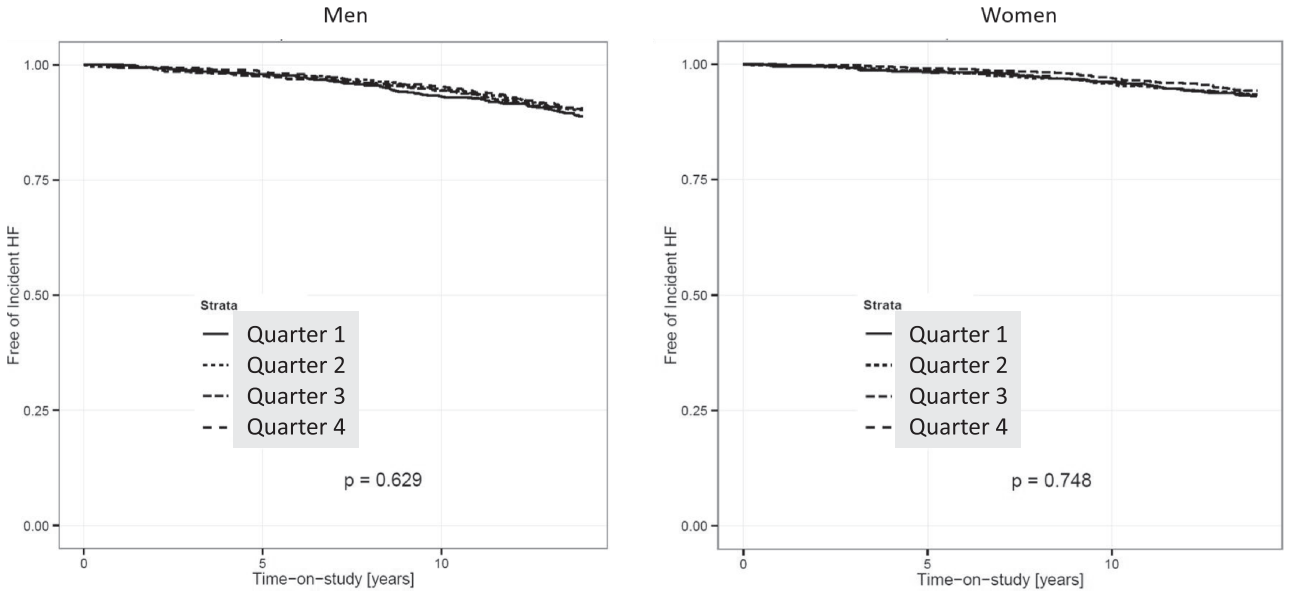
Table 3 Hazard ratios (95% CI) of baseline serum testosterone levels with incident heart failure during follow-up

	Quarter 1 (highest)	Quarter 2	Quarter 3	Quarter 4 (lowest)	*P*-value
			HR (95% CI)		
Men					
Model 1	1	1.22 (0.86–1.73)	1.21 (0.86–1.69)	1.51 (1.09–2.10)	0.020
Model 2	1	1.11 (0.78–1.58)	0.93 (0.65–1.31)	0.99 (0.70–1.42)	0.77
Women					
Model 1	1	0.64 (0.44–0.93)	0.81 (0.58–1.14)	0.70 (0.49–0.98)	0.086
Model 2	1	0.77 (0.52–1.12)	1.04 (0.73–1.48)	0.92 (0.64–1.33)	0.99

CI, confidence interval; HR, hazard ratio.
Model 1: age was used as timescale, adjusted for geographical region. Model 2: additionally adjusted for total cholesterol (log), high-density lipoprotein cholesterol (log), systolic blood pressure (log), known hypertension, known diabetes, smoking status, waist-to-hip ratio, body mass index, and time period of blood drawn.

Figure 1 Age-adjusted Kaplan–Meier curves for the endpoint incident heart failure according to quarters of baseline testosterone. HF, heart failure.



focused on its effects on cardiometabolic disease.[2–4,30] Here, we evaluated the predictive value of serum testosterone levels for the incidence of heart failure in men and in women.

Heart failure is an age-dependent disease, showing a clear sex-specific incidence, thereby hinting to a possible causality between endogenous sex hormones and disease development.[1] Male sex is considered a major risk factor for heart failure, and a potential decline in testosterone levels with increasing age is widely discussed.[2,31] Accordingly, sex-stratified Cox regression analyses, taking age into account, yielded a quite strong association between low testosterone and incident heart failure. Nevertheless, our current data of a large European population failed to demonstrate an association between low testosterone levels and the development of heart failure beyond adjustment for WHR and BMI. By its strict methodological approach, its prospective design with long-term follow-up of almost 14 years, a large sample size, and the inclusion of women, our study delivers very strong evidence on the relevance of low testosterone levels regarding future heart failure.

These results seem surprising in view of two previous reports of the FINRISK97 study, linking the established risk factors of heart failure, BMI, diabetes, and also atrial fibrillation and stroke in men, with low serum testosterone.[2,3] Our results reflect rigorous adjustment for conventional cardiovascular risk factors, which are independently associated with testosterone status. Moreover, our report is in contrast to a very recent report from the ARIC study: the authors found a statistically significant association between testosterone and incident heart failure in a general American community.[6] The HR for heart failure associated with 1-SD decrease in log-transformed total testosterone was 1.10 (95% CI: 1.03–1.17) in men and 1.05 (95% CI: 0.99–1.13) in women, respectively. In subanalyses, the associations between testosterone with subtypes of heart failure, heart failure with preserved ejection fraction, and heart failure with reduced

ejection fraction had similar patterns but were attenuated and became statistically insignificant. The authors conclude that similar directions of association in both sexes and both subtypes suggest that sex hormones play a role in the development of heart failure through common pathways regardless of sex. We could not confirm this borderline finding in our study, which might be due to three differences between the both studies—two equally large studies with clearly longer than a decade of follow-up: (i) two different populations—a Northern European and a North American, which is much more heterogeneous in terms of ethnicities; (ii) a different statistical approach, with a distinct adjustment for potential confounders—and possibly an overadjustment with BMI and WHR, in the FINRISK97 study; and (iii) and most importantly, the ARIC population is much older—a mean age of 63 vs. 47 years. It might be that the detrimental effects of low testosterone take decades to impair heart function and might not be covered by the follow-up of almost 14 years in the present study. This is also reflected in the fact that testosterone is predictive of classical risk factors, but not for heart failure itself. Regardless of the ARIC study, one may also hypothesize that testosterone acts as neutral bystander in cardiometabolic disease, and especially in the development of heart failure, and more common factors, like atherosclerosis, poor physical fitness, or increased body fat, BMI, and WHR, reduce testosterone concentrations and thereby confound the risk of heart failure. Accordingly, it was shown that increased abdominal adiposity causes elevated aromatase levels, which lower the availability of pituitary gonadotrophins and activate the conversion of testosterone to estradiol.[32]

Taken together, we did not find an independent association, and even the association found in the ARIC study seems very minor and most probably does not justify a therapeutic intervention.

Study limitations

Several limitations need to be addressed: first, we did no serial sampling. We therefore cannot explore the impact of changes in testosterone concentrations towards future disease development. Second, we did not measure other emerging biomarkers, which however seems negligible, because no association was found anyway. Third, samples were stored over 20 years and potential degradation cannot be excluded. However, this would have affected both cases and non-cases. Fourth, blood samples were drawn throughout the day and sexual hormones undergo circadian variation, although we adjusted for time period of blood drawn in Cox regression analyses. Fifth, Cox regression analyses, in particular Model 2, should be interpreted with caution, because of a possible overadjustment. Lastly, we did not measure other sexual hormones and thereby cannot discuss on their potential predictive value.

Conclusion

Low testosterone levels predict incident heart failure during long-term follow-up. However, this association disappears in multifactorial analyses including BMI and WHR.

Conflict of interest

V.S. has been supported by the Finnish Foundation for Cardiovascular Research. He has consulted for Novo Nordisk and Sanofi and received honoraria from these companies. He also has ongoing research collaboration with Bayer Ltd. S.B. has received research funding from Boehringer Ingelheim, Bayer Healthcare, Abbott Diagnostics, Siemens, Thermo Fisher, and Roche Diagnostics and received honoraria for lectures or consultation from Boehringer Ingelheim, Bayer, Roche, AstraZeneca, Siemens, Thermo Fisher, and Abbott Diagnostics. M.K. has received research funding from Vifor Pharma, Daiichi-Sankyo, and Adrenomed AG and received honoraria for lectures or consultation from AstraZeneca, Amgen, Sanofi-Aventis, Adrenomed, Sphingotec, and Vifor Pharma. All other authors declare no conflict of interest. M.K. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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