Prediction of Metabolic Syndrome by Low Serum Testosterone Levels in Men
Results From the Study of Health in Pomerania

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OBJECTIVE—The aim of this analysis was to assess the prospective association of serum testosterone and dehydroepiandrosterone sulfate (DHEAS) levels with incident metabolic syndrome (MetS) in men.

RESEARCH DESIGN AND METHODS—Data were obtained from the Study of Health in Pomerania (SHIP), a population-based prospective cohort of adults aged 20–79 years. Analyses were conducted in 1,004 men without baseline MetS defined by National Cholesterol Education Program Adult Treatment Panel III guidelines. Testosterone and DHEAS were categorized by age-specific quartiles and Poisson regression models with relative risks (RRs) and 95% CIs were estimated.

RESULTS—After a median follow-up time of 5.0 years, 480 men (47.8%) developed MetS. Testosterone levels decreased with increasing number of MetS components. Testosterone in the lowest quartile predicted MetS (RR 1.38 [95% CI 1.13–1.69]), particularly among men aged 20–39 years (2.06 [1.29–3.29]), even after adjustment for age, smoking, alcohol consumption, physical activity, waist circumference, self-related health, and time of blood sampling. DHEAS levels were not related to incident MetS (0.99 [0.83–1.19]).

CONCLUSIONS—Low testosterone but not DHEAS predicts development of MetS in a population-based cohort of 1,004 men aged 20–79 years. Especially in young men aged 20–39 years, results suggest low testosterone as a strong predictor for incident MetS. Assessment of testosterone in young and middle-age men may allow early interventions in the general population.
TABLE 1
Baseline characteristics of men by full and analytical sample

| Variable                        | Full sample | Analytical sample | Without MetS at follow-up | Incident MetS at follow-up |
|---------------------------------|-------------|-------------------|---------------------------|---------------------------|
| n                               | 2,117       | 1,004             | 524                       | 480                       |
| Age (years)                     | 51.3 ± 16.6 | 48.7 ± 15.9*      | 45.6 ± 15.7               | 51.9 ± 15.5*              |
| Total testosterone (nmol/l)     | 15.9 (12.7–20.1) | 16.6 (13.4–20.6)* | 17.7 (14.4–21.5)         | 15.5 (12.6–19.1)*         |
| DHEAS (µg/dl)                   | 1.63 (0.96–2.56) | 1.74 (1.09–2.69)* | 1.98 (1.25–2.83)         | 1.58 (0.94–2.52)*         |
| Daily alcohol consumption (g/day)| 11.9 (1.5–28.2) | 13.6 (2.5–28.9)   | 16.5 (2.7–30.3)          | 10.0 (0.0–27.2)*          |
| Riskful alcohol consumption     | 23.0        | 23.9              | 25.2                      | 22.5                      |
| Self-related health             |             |                   |                           |                           |
| Very good                       | 2.1         | 2.3*              | 2.5                       | 2.1*                      |
| Good                            | 15.4        | 19.1*             | 21.4                      | 16.7*                     |
| Fair                            | 64.0        | 64.6*             | 66.4                      | 62.7*                     |
| Poor/very poor                  | 18.4        | 13.9*             | 9.7                       | 18.5*                     |
| Smoking                         |             |                   |                           |                           |
| never smoker                    | 21.0        | 24.2*             | 26.5                      | 21.7                      |
| ex-smoker                       | 45.3        | 42.2*             | 39.3                      | 45.4                      |
| current smoker                  | 33.7        | 33.6*             | 34.2                      | 32.9                      |
| Physical activity               | 41.0        | 46.7*             | 50.4                      | 42.7*                     |
| BMI (kg/m²)                     | 27.6 ± 4.0  | 26.4 ± 3.3*       | 25.5 ± 3.2                | 27.4 ± 3.0*               |
| Waist circumference (cm)        | 102.0 (97.6–107.2) | 100.3 (96.4–104.3)* | 98.8 (94.8–103.3)        | 101.9 (98.3–105.7)*       |
| Systolic blood pressure (mmHg)  | 143.6 ± 19.5 | 139.2 ± 17.9*     | 134.6 ± 16.3              | 141.2 ± 17.8*             |
| Diastolic blood pressure (mmHg) | 86.3 ± 11.3 | 85.0 ± 10.9*      | 83.0 ± 10.8               | 86.8 ± 10.4*              |
| Hypertension                    | 62.4        | 59.8*             | 56.1                      | 63.8                      |
| Glucose (mmol/l)                | 5.9 ± 1.9   | 5.4 ± 1.3*        | 5.2 ± 0.63                | 5.6 ± 1.7*                |
| Triglycerides (mmol/l)          | 2.13 ± 1.61 | 1.77 ± 1.42*      | 1.41 ± 0.83               | 2.12 ± 1.80               |
| HDL cholesterol (mmol/l)        | 1.30 ± 0.37 | 1.38 ± 0.34*      | 1.49 ± 0.35               | 1.28 ± 0.28               |
| Diabetes                        | 8.8         | 7.2*              | 6.7                       | 7.7                       |
| Dyslipidemia                    | 62.0        | 56.5*             | 33.4                      | 81.7                      |

Data are percentages, means ± SD, or medians (interquartile range). To convert the values of serum testosterone to ng/dl multiply by 28.82. To convert the values of serum DHEAS to μmol/l multiply by 0.027. *P < 0.05 using χ² test (nominal data) and Wilcoxon test (continuous data) for bivariate comparisons between analytical sample and full sample as well as between subjects with and without metabolic syndrome at follow-up, respectively.

RESULTS
After a median follow-up time of 5.0 years (range 4.4–8.3), 480 men (47.8%) developed MetS. The analytical sample appeared to be healthier than the full sample, whereas men with incident MetS were significantly older, exposed to lower testosterone and DHEAS levels, scored worse for self-related health, were physically less active showed higher body fat accumulation, and exposed significant differences in all MetS components than men without incident MetS (Table 1). We detected an overall trend of increasing risk of incident MetS with decreasing levels of both testosterone and DHEAS in unadjusted analyses (Table 2). The risk of incident MetS was highest for men with baseline testosterone and DHEAS levels in the lowest quartile (unadjusted RR 1.52 [95% CI 1.25–1.85]) and 1.38 [1.16–1.65] respectively) than the highest quartile. P for trend statistics revealed that RRs were also linearly elevated (P for trend < 0.001). Stratifying analyses by 20-year
DISCUSSION

Our results from a population-based sample of 1,004 men aged 20–79 years reveal an inverse association between baseline testosterone and the development of MetS independent of important confounding factors. Especially in young men aged 20–39 years, low testosterone was a strong predictor for incident MetS. Baseline DHEAS did not show an independent prospective association with incident MetS. The association of low testosterone not only with components of MetS but also with MetS itself was previously reported from different cross-sectional studies in varying populations (2,3,5) as well as from longitudinal studies (4). Our finding of an independent prospective association of testosterone with MetS in young men aged 20–39 years has not been reported previously. Most remarkably, the association appeared to be stronger in young and middle-aged men than in the elderly.

Although the temporal sequence of low testosterone preceding the development of MetS suggests a causal relationship between the two phenomena, we cannot TABLE 2

| Quartiles of total testosterone | All men | 20–39 years of age | 40–59 years of age | 60–79 years of age |
|--------------------------------|---------|---------------------|---------------------|---------------------|
| 25th                           | 1.52 (1.25–1.85)§ | 2.50 (1.58–3.96)§ | 1.41 (1.06–1.89)†  | 1.15 (0.86–1.54)  |
| 25–50th                        | 1.41 (1.15–1.72)‡ | 2.20 (1.38–3.53)‡ | 1.30 (0.96–1.75)  | 1.13 (0.84–1.52)  |
| 50–75th                        | 1.14 (0.92–1.42)  | 1.38 (0.82–2.34)   | 1.04 (0.75–1.45)  | 1.15 (0.86–1.54)  |
| 75th                           | 1.00 (ref.)       | 1.00 (ref.)        | 1.00 (ref.)       | 1.00 (ref.)       |

P for trend

| All men | 20–39 years of age | 40–59 years of age | 60–79 years of age |
|---------|---------------------|---------------------|---------------------|
| Quartiles of DHEAS | 1.38 (1.16–1.65)§ | 0.89 (0.61–1.30)   | 1.06 (0.79–1.40)   |
| 25–50th                        | 1.23 (1.02–1.47)† | 0.74 (0.49–1.11)  | 1.09 (0.82–1.44)   |
| 50–75th                        | 0.98 (0.80–1.19)  | 1.00 (0.70–1.43)  | 0.98 (0.72–1.32)   |
| 75th                           | 1.00 (ref.)       | 1.00 (ref.)        | 1.00 (ref.)        |

P for trend

| All men | 20–39 years of age | 40–59 years of age | 60–79 years of age |
|---------|---------------------|---------------------|---------------------|
| Adjusted RR (95% CI) | 2.06 (1.29–3.29)‡ | 1.34 (1.00–1.81)† | 1.00 (0.75–1.37)   |

Fig. 1. Means with 95% CI in the analytical sample (n = 1,004) for total testosterone levels according to zero, one, two, three, four, or more MetS components. A significant trend of decreasing testosterone with increasing number of MetS components was observed (P < 0.001 for trend).
prove whether low testosterone contributes to or is a very early consequence of mechanisms finally leading to MetS. There is evidence for both views because, on the one hand, weight loss in obese men and in men with MetS increased free and total testosterone as well as sex hormone–binding globulin levels (16) and, on the other hand, interventional studies with testosterone in men with low serum levels decreased fat mass, total cholesterol, and LDL cholesterol (17,18). Thus, the possibility exists that there is a vicious cycle between low testosterone and metabolic alterations leading to MetS and consequently contributing to more severe complications such as type 2 diabetes and CVD. Given reports of greatly increased MetS prevalence in hypogonadism from Klinefelter’s syndrome with little effect of testosterone treatment on body composition (19) and higher cardiovascular risk among men undergoing long-term androgen-deprivation therapy (20), we recommend interventional studies of exogenous testosterone supplementation in men with MetS to further delineate the causal relationship of testosterone and MetS.

The present findings suggest that DHEAS is not associated with MetS. Although previous observational studies were able to detect an association of DHEAS and ischemic heart disease (21), the clinical significance of DHEAS in CVD remains uncertain (22). So, the possibilities to explain why in our study testosterone is a predictor of MetS whereas DHEAS is not are broad, ranging from differences in study population’s age structure, time of blood sampling, or laboratory methodology. However, data from prospective randomized trials are needed to illuminate the basic physiological role of DHEAS in CVD and to clarify whether DHEAS supplementation has any cardiovascular benefit.

Limitations arise from the lack of measured free testosterone, sex hormone–binding globulin, or albumin for calculation of bioavailable testosterone as well as from single measurement of testosterone. Due to logistical impossibilities, we used nonfasting blood samples for the definition of MetS. However, because differences between fasting and nonfasting participants are reported to be negligible (23), fasting status is unlikely to cause associations. In summary, our results suggest that testosterone may serve as an early indicator for future metabolic risk. Therefore, further studies should examine whether testo-

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**FIG. 2.** Means with 95% CI in the analytical sample (n = 1,004) for DHEAS levels according to zero, one, two, three, four, or more components of MetS at baseline by 20-year age-groups. To convert the values of serum DHEAS to μmol/l multiply by 0.027.
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