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CLINICAL STUDY

A cohort effect on serum testosterone levels in Finnish men

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Abstract

Objective: To investigate whether a population-level decline in serum testosterone exists in Finnish men. In comparison with other European populations, Finnish men have compared well in the studies of reproductive health (i.e. semen quality, incidence of cryptorchidism and testicular cancer); thus, we expected no significant cohort-dependent decrease in serum testosterone.

Methods: We analysed serum levels of testosterone, gonadotrophin and sex hormone binding globulin (SHBG) in 3271 men representing different ages (25–74 years) and birth cohorts within three large Finnish population surveys conducted in 1972, 1977 and 2002.

Results: Serum testosterone levels decreased (from 25.3 nmol/l in 25- to 29-year-old men gradually to 16.9 nmol/l in 70- to 74-year-old men), whereas SHBG and gonadotrophin levels increased with increasing age. In addition, a significant secular trend in testosterone (total and free), SHBG and gonadotrophin levels was observed with lower levels in more recently born age-matched men. Serum testosterone level decreased in men aged 60–69 years from 21.9 nmol/l (men born 1913–1922) to 13.8 nmol/l (men born 1942–1951). These decreases remained significant following adjustment for BMI. An age-independent birth cohort effect existed on reproductive hormones measured in the Finnish men. In concert with the lower free testosterone levels, we observed lower gonadotrophin levels, suggesting that while there may be detrimental changes at the gonad level, the hypothalamus–pituitary–axis is not responding appropriately to this change.

Conclusions: The more recently born Finnish men have lower testosterone levels than their earlier born peers. This study offers no explanation for this substantial recent adverse development.

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Introduction

Serum testosterone decreases with age in men, and longitudinal estimates of this phenomenon are significantly greater than cross-sectional estimates (1, 2, 3). Low serum testosterone has been associated with a number of compromised health conditions such as obesity, diabetes, dyslipidemia, decreased bone and muscle mass and decreased quality of life (4). The number of elderly men will significantly increase in the near future and hence their well-being and quality of life are of general concern for public health. Two recent studies reported a population-level decline in serum testosterone in American and Danish men (5, 6). This would partly explain the observed difference in age-related serum testosterone decline between cross-sectional vs longitudinal studies, and it may also reflect an ongoing adverse trend in male reproductive health. By contrast, the recent analysis of National Health and Nutritional Examination Surveys (NHANES) from 1988 to 1991 and from 1999 to 2004 failed to show any decline in testosterone in USA males (7).

Compared with Danishmen, the Finnish men have compared well in recent evaluations of reproductive health (i.e. incidence of cryptorchidism, hypospadias and testicular cancer and semen quality) (8, 9, 10, 11, 12); we questioned whether population-level changes in testosterone levels would also be apparent in Finnish men and therefore not specific to men from Denmark and New England.

Subjects and methods

Study population

Testosterone, gonadotrophin and sex hormone binding globulin (SHBG) were analysed in sera of men from three Finnish population surveys conducted in 1972, 1977 and 2002 by the National Public Health Institute (presently the National Institute for Health and Welfare). Data collection and blood sampling were carried out within the national cardiovascular disease risk factor surveys named the National FINRISK

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Study (13). For each survey, an independent random sample was drawn from the national population register, i.e. the same individuals did not contribute to different surveys. To obtain comparable data, the methodology of the data collection has been kept as similar as possible throughout the survey years. Since 1982, the survey methodology has closely followed the WHO MONICA protocol (14). In 2002, some more detailed recommendations of the European Health Risk Monitoring Project were adopted (15). The surveys included a self-administered questionnaire, physical measurements and blood tests. The health questionnaire, together with the invitation to the health examination, was sent by mail to all the selected subjects. Trained nurses carried out the physical measurements and blood sampling in the local health centres.

Venous blood samples were drawn during office hours following a minimum of 4-h fasting. Samples were then centrifuged in the field survey sites and the sera were mailed daily to the Laboratory of Analytical Biochemistry in the National Public Health Institute. Upon arrival, they were immediately frozen and later stored at −20 °C. For this study, we received serum samples from this Bio bank from 3271 men. The men were divided into six age groups: 25–29, 30–39, 40–49, 50–59, 60–69 and 70–74 years). They were also divided into seven birth cohort groups according to their year of birth: 1913–1922, 1923–1932, 1933–1941, 1942–1951, 1952–1959, 1960–1969 and 1970–1977. The number of men in each category in the age–birth year matrix is shown in Table 1. Although the number of men in each cell is quite different, the distribution of ages within each age group and cell is rather even.

Hormone measurements

Testosterone, SHBG, LH and FSH levels were measured by time-resolved fluoroimmunoassays (DELFIA; Wallac Oy, Turku, Finland) with detection limits 0.23, 0.23 nmol/l, 0.05 and 0.06 IU/l respectively. The intra- and interassay coefficients of variation were <12% for testosterone, 8% for SHBG and 5% for gonadotrophins.

All samples were analysed during the same period and mixed in the different assay runs to eliminate any influence of assay variation. Free testosterone was calculated from the testosterone and SHBG concentrations using the method by Vermeulen *et al.* (16), with the assumption of an average serum albumin concentration of 43 g/l.

Statistical analysis

Hormone levels across age and birth cohort groups were compared using one-way ANOVA with Bonferroni's *post hoc* test. The effect of age, BMI and birth cohort on the hormone levels was compared using multiple regression models adjusting for the other respective variables.

Ethics

The study was approved by the Joint Ethics Committee of the Turku University and Turku University Central Hospital.

Table 1 Number of participants in each age and cohort group and the respective serum testosterone concentrations in nanomoles per litre (median, 5th–95th percentiles) in birth cohorts of Finnish men.

Birth year	1970–1977	1960–1969	1952–1959	1942–1951	1933–1941	1923–1932	1913–1922	All
Age (years)								
25–29	*n*=63 19.1 (8.7–27.3)			*n*=289 26.4‡ (15.1–44.0)				*n*=352 25.3 (13.3–43.5)
30–39	*n*=51 17.2 (7.7–37.6)	*n*=127 16.1 (8.6–28.3)		*n*=57 20.5*,‡ (11.1–38.6)	*n*=624 22.0‡ (11.6–38.6)			*n*=859 20.5* (10.3–37.6)
40–49		*n*=62 15.7 (7.5–25.8)	*n*=143 14.6 (8.5–29.8)			*n*=682 22.6‡ (11.2–39.6)		*n*=887 20.9* (9.5–38.4)
50–59			*n*=28 17.4 (8.7–30.9)	*n*=204 15.3*,† (7.5–30.4)			*n*=519 22.6‡ (11.3–40.9)	*n*=751 19.9* (8.7–39.9)
60–69				*n*=23 13.8*,† (7.7–27.8)	*n*=192 14.4 (8.0–31.3)		*n*=130 21.9‡ (10.3–40.9)	*n*=345 17.0*,† (8.1–36.4)
70–74						*n*=77 16.9 (8.4–28.3)		*n*=77 16.9*,† (8.4–28.3)

*,†Depict statistical significance compared with the above values in each column. ‡,§Depict statistical significance compared with the values to the left across each row. The significance in all of the cases is $P<0.05$.

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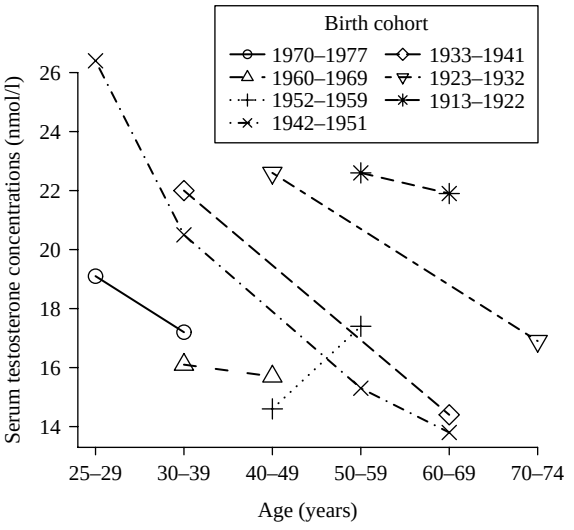

Figure 1 Serum testosterone concentrations (nmol/l; median values) in Finnish men of different ages (*X*-axis) born in different decades. Note that the *Y*-axis does not start from 0.

Results

Testosterone

Serum total testosterone concentration modestly decreased with age in the study population from on average 25.3 nmol/l in the youngest men (25–29 years) to 16.9 nmol/l in the oldest men (70–74 years). Testosterone levels declined over ages as follows: 25–29 > 30–39 = 40–49 = 50–59 > 60–69 = 70–74 years (Bonferroni's *post hoc* test). In addition to the overall age-related decrease, significantly lower serum testosterone levels were observed in men of the same age born in more recent decades. This was true in all age groups for which two or more groups existed with at least a decade's difference in time of birth (Fig. 1). For more detailed data, see Table 1.

Sex hormone binding globulin

Serum SHBG concentrations increased clearly with age in the study population: 25–29 = 30–39 < 40–49 < 50–59 = 60–69 = 70–74 years. Within age groups, a clear trend of men born earlier (at least a decade's difference) displaying higher SHBG concentrations was observed (Table 2).

Free testosterone

A more pronounced decrease was observed in serum free testosterone with age compared with the total testosterone (Table 3). The cohorts of men born earlier displayed significantly higher free testosterone concentrations, although not all pair-wise comparisons between two consecutive cohorts reached statistical significance.

Gonadotrophins

In response to the age-related decreasing testosterone, serum LH concentrations increased significantly with age in the entire study population, being highest in the oldest group (25–29 = 30–39 = 40–49 < 50–59 = 60–69 < 70–74 years). By contrast, LH did not seem to respond to the birth year-related decrease of testosterone levels, but LH levels were significantly lower in men born later (Table 4). Similarly, serum FSH concentrations showed an age-related increase (25–29 = 30–39 < 40–49 < 50–59 = 60–69 = 70–74 years), but a birth year-related decrease within age groups with lower levels was measured in the cohort born later (Table 5).

Hormone level in relation to BMI

The BMI was higher in the older men. When stratified according to age and birth cohort, serum testosterone, SHBG and LH concentrations were significantly correlated with BMI (Table 6).

Both age and BMI were statistically significant variables affecting testosterone levels ($P < 0.0001$), but the effect of birth cohort on serum testosterone remained significant when data were stratified according to age-related changes and BMI ($P < 0.0001$ in cohorts born by 1951 in comparison with 1970–1974; Table 6). However, this cohort effect is not significant when the three most recently born age groups are compared each with each other ($P = 0.0931$ and $P = 0.6625$ for men born in 1952–1959 and 1960–1979 respectively).

Table 2 Serum SHBG concentrations in nanomoles per litre (median, 5th–95th percentiles) in birth cohorts of Finnish men.

Birth year	1970–1977	1960–1969	1952–1959	1942–1951	1933–1941	1923–1932	1913–1922	All
Age (years)								
25–29	26 (15–53)			33‡ (17–57)				32 (16–56)
30–39	28 (17–59)	28 (14–50)		28 (14–54)	35‡ (17–56)			33 (16–56)
40–49		34 (14–51)	33 (19–60)			41‡ (20–75)		38* (19–72)
50–59			42* (16–66)	36* (19–71)			47‡ (24–85)	44*,† (21–81)
60–69				38 (18–78)	38* (24–84)		50‡ (26–94)	40*,† (22–91)
70–74						50* (26–77)		50*,† (26–77)

*,†Depict statistical significance compared with the above values in each column ($P < 0.05$, ANOVA). ‡,§Depict statistical significance compared with the values to the left across each row.

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Table 3 Serum free testosterone concentrations in picomoles per litre (median, 5th–95th percentiles) in birth cohorts of Finnish men.

Birth year	1970–1977	1960–1969	1952–1959	1942–1951	1933–1941	1923–1932	1913–1922	All
Age (years)								
25–29	410 (212–704)			610$^{\|}$ (350–1010)				570 (310–1000)
30–39	390 (170–675)	370 (190–587)		490 (280–986)	470 (270–859)			450* (240–840)
40–49		320 (172–607)	320 (190–617)			430$^{\|}$ (240–720)		400*,† (220–710)
50–59			330 (174–523)	285* (160–490)			390$^{\|}$ (189–661)	360*,†,‡ (170–630)
60–69				270* (181–509)	260* (8.0–31.3)		370$^{\|}$ (190–620)	310*†,‡,§ (160–558)
70–74						260* (158–450)		260*,†,‡,§ (158–450)

*,†,‡,§Depict statistical significance compared with the above values in each column ($P<0.05$, ANOVA). $^{\|,\P}$Depict statistical significance compared with the values to the left across each row.

Likewise, the cohort effect on serum LH, FSH and SHBG levels is significant in cohorts born earlier when data were stratified according to age-related changes and BMI ($P<0.0001$; Table 6). Similar to serum testosterone, the significance of the cohort effects in LH, FSH and SHBG levels is lost in the more recently born men (Table 6).

Discussion

In this study, we observed a clear age- and BMI-independent birth cohort effect on serum testosterone concentrations measured in Finnish men. Our study is the third large population study to demonstrate a declining trend in serum testosterone of men in a similar fashion as seen in a USA and Danish population. Men born more recently have also been shown to have a higher risk of testicular cancer compared with men born in previous decades (17). Furthermore, several studies have indicated that sperm concentrations among men in Europe have decreased (18). Taking these findings together with the cohort effect observed in this and the previous studies, serum testosterone concentrations appear to follow a similar pattern and these changes together may well reflect a detrimental change in the overall reproductive health in men.

Finnish men have previously displayed better reproductive health compared with Danish men as they show better semen quality (9, 10) and markedly lower incidences of testicular cancer (19), cryptorchidism and hypospadias (8, 11, 12). If the cohort effect in serum testosterone levels observed in Danish men reflects their overall reproductive health (5), the Finns would be expected to show little or no cohort effect. This, however, was not the case, as the cohort effect we observed in the Finnish men was as evident as previously observed in other countries including Denmark (5, 6). Thus, although the reproductive health of Finnish men may be better compared with Danish men judged by the above-mentioned criteria, a birth cohort-related decrease in serum testosterone levels seems to have taken place over several decades. More recent data on reproductive health of Finnish men show that the

Table 4 Serum LH concentrations in international units per litre (median, 5th–95th percentiles) in birth cohorts of Finnish men.

Birth year	1970–1977	1960–1969	1952–1959	1942–1951	1933–1941	1923–1932	1913–1922	All
Age (years)								
25–29	3.16 (1.67–5.14)			3.85‡ (1.81–7.96)				3.74 (1.79–7.65)
30–39	3.32 (1.01–6.2)	3.28 (1.35–8.41)		3.99‡ (1.75–7.28)	3.80‡ (1.74–7.63)			3.76 (1.6–7.48)
40–49		3.60 (1.41–5.78)	3.42 (1.67–7.96)			4.10‡ (1.9–9.17)		3.91 (1.86–9.05)
50–59			3.67 (1.98–7.78)	3.91 (1.61–8.11)			4.87‡ (2.04–12.6)	4.53* (1.95–11.44)
60–69				4.57* (1.81–9.53)	4.40* (2.01–10.28)		5.51*,‡ (2.21–18.34)	4.73* (2.06–12.86)
70–74						5.57* (2.28–11.61)		5.57*,† (2.28–11.61)

*,†Depict statistical significance compared with the above values in each column ($P<0.05$, ANOVA). ‡,§Depict statistical significance compared with the values to the left across each row.

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Table 5 Serum FSH concentrations in international units per litre (median, 5th–95th percentiles) in birth cohorts of Finnish men.

Birth year	1970–1977	1960–1969	1952–1959	1942–1951	1933–1941	1923–1932	1913–1922	All
Age (years)								
25–29	3.17 (1.5–5.9)			3.60‡ (1.42–11.24)				3.43 (1.47–10.85)
30–39	3.12 (1.37–6.61)	3.58 (1.4–7.7)		3.49 (1.72–11.42)	4.21‡ (1.74–10.66)			4.00 (1.66–10.31)
40–49		3.72 (1.58–9.25)	3.92 (2.04–11.14)			4.92‡ (2.17–16.3)		4.56* (2.05–15.17)
50–59			3.71 (1.97–8.65)	4.58* (1.97–11.58)			6.52‡ (2.4–23.7)	5.64*,† (2.2–18.84)
60–69				6.05*,† (2.67–25.82)	5.60* (2.03–17.43)		6.37 (1.46–21.36)	5.92*,† (2.02–18.68)
70–74						6.43 (2.88–27.13)		6.43*,† (2.88–27.13)

*,†Depict statistical significance compared with the above values in each column ($P<0.05$, ANOVA). ‡,§Depict statistical significance compared with the values to the left across each row.

incidence of testicular cancer has increased and the semen quality has decreased in the more recently born Finnish men (20). Together, these observations suggest that the adverse trends in the parameters of reproductive health may have lagged behind in the Finnish men compared with e.g. Danish men, but that the same trends nevertheless occur in Finland. Changes in serum testosterone may be an early sentinel for adverse trends in reproductive health as the decline in serum testosterone was also observed between the earliest birth cohorts included in this study.

Several studies have shown that serum testosterone concentration decreases in men with ageing. The cross-sectional studies report a decrease of $<1\%$/year, whereas a more dramatic decrease is observed in the longitudinal studies (21). Our current study is well in agreement with these findings as, the decrease of serum testosterone is of similar magnitude. The magnitude of the cohort effect is similar when comparing different cohorts within each age group (2–4 nmol/l per decade). Although greater in magnitude, the changes in calculated serum free testosterone reflect the changes in total testosterone.

In our study population, the gonadal–pituitary feedback system reacted appropriately to the age-related decrease in serum testosterone, with a typical increase in LH levels. Analysis of all the age groups (irrespective of birth decade) supports the compensatory age-dependent LH increase associated with decreasing testosterone in our study. But, within each age group,

Table 6 The effect and significance of age, BMI and birth cohort studied in multivariate regression models adjusted for the other two respective factors. The study population is divided into seven birth cohorts by their birth years. In the analyses, the birth cohorts are compared with the most recent birth cohort (individuals born in 1970–1974); hence, this is the point of reference and given value 1 (significant comparisons are highlighted by bolding, with the respective *P* value below).

Variables	Testosterone ($\beta\pm$S.E.M.)	SHBG ($\beta\pm$S.E.M.)	Free testosterone ($\beta\pm$S.E.M.)	LH ($\beta\pm$S.E.M.)	FSH ($\beta\pm$S.E.M.)
Age	**−0.182±0.015** ***P*<0.0001**	**0.432±0.027** ***P*<0.0001**	**−0.007±0.001** ***P*<0.0001**	**0.031±0.005** ***P*<0.0001**	**0.066±0.010** ***P*<0.0001**
BMI	**−0.776±0.041** ***P*<0.0001**	**−1.842±0.075** ***P*<0.0001**	**−0.006±0.001** ***P*<0.0001**	**−0.069±0.015** ***P*<0.0001**	**−0.028±0.027** ***P*=0.294**
Birth cohort					
(1913–1922)	**9.460±0.914** ***P*<0.0001**	**8.540±1.687** ***P*<0.0001**	**0.164±0.019** ***P*<0.0001**	**1.900±0.337** ***P*<0.0001**	**3.176±0.596** ***P*<0.0001**
(1923–1932)	**6.957±0.853** ***P*<0.0001**	**5.425±1.573** ***P*=0.0006**	**0.125±0.017** ***P*<0.0001**	**0.847±0.314** ***P*=0.0071**	**2.048±0.556** ***P*=0.0002**
(1933–1941)	**4.969±0.828** ***P*<0.0001**	1.552±1.528 *P*=0.310	**0.109±0.017** ***P*<0.0001**	**0.599±0.305** ***P*=0.050**	**1.427±0.540** ***P*=0.0008**
(1942–1951)	**4.947±0.839** ***P*<0.0001**	0.979±1.549 *P*=0.527	**0.120±0.017** ***P*<0.0001**	**0.636±0.309** ***P*=0.040**	0.974±0.548 *P*=0.076
(1952–1959)	1.692±1.007 *P*=0.093	−1.199±1.858 *P*=0.519	**0.041±0.020** ***P*=0.044**	0.050±0.371 *P*=0.894	0.204±0.657 *P*=0.756
(1960–1979)	−0.420±0.964 *P*=0.663	−2.659±1.779 *P*=0.135	−0.001±0.020 *P*=0.950	0.056±0.355 *P*=0.874	−0.032±0.629 *P*=0.959
(1970–1974)	1	1	1	1	1

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the more recently born men with lower testosterone also displayed lower LH levels. Obese ageing men may display signs of hypogonadotrophic hypogonadism, perhaps due to the feedback effect of adipose tissue-derived oestrogen (3). Unfortunately, we did not have oestradiol measurements of these samples. However, although the later-born cohorts in our study had higher BMIs, this alone could not explain the relative decline in gonadotrophin levels in later birth cohorts. Previous studies have not reported gonadotrophin levels in association with the testosterone changes. It is clear that this birth cohort effect makes the evaluation of both cross-sectional and longitudinal studies more complex. Health consequences of the declining testosterone levels would be associated with deteriorating reproductive health. The reasons for these changes need to be identified in order to prevent reproductive problems. Furthermore, several studies have shown that decreased serum testosterone levels are associated with increased morbidity and adverse health conditions (4, 22). Our finding reflects a relative decrease in serum testosterone on a population level, and the values for most men remain well within the normal reference range. However, a shift of the total population will consequently increase the number of individuals who become hypogonadal and experience effects of low testosterone, particularly with increasing age.

Unfortunately, in a cohort study of this nature, it was not possible to ensure similar group size in the different age groups or in the different cohort groups. Whereas our study population is relatively large, the small size of some groups weakens the statistical power and makes the analysis of these groups less reliable. Collection of the blood samples for testosterone analysis should optimally be performed during the morning hours. Variable collection times may affect individual testosterone levels. However, as the samples were collected similarly in the different surveys, this is very unlikely to have affected the cohort effect studied.

Our study cannot reveal the causes of the adverse trends in male reproductive hormone levels. However, the fact that the changes occurred over a relatively short period suggests that changes in lifestyle or environment – or both – are involved. The reasons for these changes need to be identified in order to prevent further deterioration of male reproductive health.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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