Secular trends in testosterone- findings from a large state-mandate care provider

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Abstract

Background

Several studies from the US and Europe have shown a population-level decline in serum testosterone in men from 1970's to early 2000's. However, to the best of our knowledge, no study examining population-level decline in testosterone has been published in more recent years. The study objective was therefore to examine secular trends in testosterone levels among Israeli men in the first and second decades of the 21st century.

Methods

All incident total testosterone performed between 1/2006 and 3/2019 among 102,334 male members of a large health organization.

Results A prominent trend of age-independent decline in the testosterone levels for most age groups. The results were highly significant.

Conclusions

The results show a highly significant age-independent decline in total testosterone that is unlikely to be explained by increasing rates of obesity.

Background

Testosterone plays a major role in male reproductive function, including stimulating Sertoli cell function and spermatogenesis, as well as affecting non-reproductive organs such as muscle growth, stimulating bone mineralization, erythropoiesis, and cognitive function(1-3).

Several studies from the US(4, 5) and Nordic countries (6, 7) have shown a significant decline in serum testosterone among men from 1970s to early 2000s. However, to the best of our knowledge, no such data were published after 2004. Changes in lifestyle and
health indices have been associated with declining testosterone, free testosterone, and SHBG levels, including body weight gain(5) and smoking cessation(5, 8). Since the decline in testosterone levels seem to be affected by modifiable risk factors, the objectives of the current study were to assess long term trends over recent decades in testosterone levels in men.

Methods

This cross sectional study was conducted in Maccabi Healthcare Services (MHS), the second largest health organization maintenance in Israel, serving 25% of the total population countrywide (2.3 million members). According to the 1994 Israel National Health Act, MHS may not bar applicants on any grounds, including age or state of health. Thus, all sectors of the Israeli population are represented in MHS, except for young adults aged 18–21, since a high percentage of them are enlisted in the Israeli Defense Forces (IDF), and receive medical care there. Membership retention rate in MHS is very high (less than 1% is leaving the organization annually) allowing for a long retrospective follow-up with a minimal lost to follow-up.

Testosterone tests

We pulled data on all the blood test measures of total testosterone (Current Procedural Terminology, 4th Edition code 84002) performed on men aged 13–80 between the years 1/2006-3/2019. Included in the analysis were only the first blood sample taken from each patient ever since 2000. We additionally filtered the data such that all included samples have the same lab norms (8.4–28.7 nanomole/liter), to ensure that all the samples were measured using the same lab methods (all the blood tests in Maccabi are analyzed at a single central lab).

Statistical methods
The study protocol has been approved by the Maccabi Healthcare Service’s institutional review board. Differences in age-specific mean BMI between decades were compared using $\eta^2$, a measure of effect size using analysis of variance (ANOVA). To test the significance of the year as a contributing factor to the testosterone level beyond age we fit a quadratic model for the age and a linear model for the measurement year (testosterone level = 1 + age + $\text{age}^2 + \text{age}^3 + \text{age}^4 + \text{year}$, the quadratic model was used for age due to the strictly non-linear behavior of testosterone as a function of age in the range 13-80). All analyses were conducted using IBM-SPSS ver. 25 and R (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2018).

Results

The final analysis was performed on a total of 102,334 eligible patients (mean age 45.6, SD = 17.3, Table 1). No meaningful differences in BMI ($\eta^2 = 0.001$) or in exact age ($\eta^2 = 0.004$) between study periods were observed. Age-specific testosterone levels over the observation period are depicted in Fig. 1A. At age 21, at testosterone peak level, levels declined from 19.68 in 2006-9 to 17.76 in 2016-19. Figure 1B presents the full distribution of age-specific testosterone values by time period (estimated using kernel density estimation). Both show a prominent trend of age-independent decline in the testosterone levels for most age groups. The results were highly significant ($p$ - value < 0.001). In addition, to account for the imperfect polynomial fit we fit a linear model (testosterone level = 1 + age + year) separately for the ages range 13-22,23-35 and 36-80 where the behavior of the testosterone level as a function of age is approximately linear, with similarly significant results ($p$ - value < 0.001)).
Table 1
Mean BMI and age of study population by period

| Age group | Period  | n  | Mean  | SD   | n  | Mean  | SD   | n  | Mean  | SD   | n  | Mean  | SD   |
|-----------|---------|----|-------|------|----|-------|------|----|-------|------|----|-------|------|
|           | 2006-9  |    |       |      |    |       |      |    |       |      |    |       |      |
| 13-18     | 1979    |    | 14.66 | 1.35 | 1900| 14.76 | 1.344| 2374| 14.77 | 1.336| 2890| 14.71 | 1.336|
| 18-24     | 1163    | 21.40 | 2.11 | 1549 | 21.56 | 2.079| 1992 | 21.38 | 2.107| 2570 | 21.52 | 1.993|
| 25-34     | 3400    | 30.10 | 2.82 | 3749 | 29.8 | 2.828| 4194 | 29.77 | 2.819| 5448 | 29.56 | 2.859|
| 35-44     | 3643    | 39.29 | 2.86 | 4000 | 39.67 | 2.835| 4999 | 39.88 | 2.848| 5568 | 39.83 | 2.919|
| 45-54     | 3795    | 49.61 | 2.83 | 5815 | 49.66 | 2.859| 6018 | 49.56 | 2.837| 7917 | 49.57 | 2.832|
| 55-64     | 3812    | 59.15 | 2.76 | 6445 | 59.48 | 2.862| 5882 | 59.45 | 2.883| 7111 | 59.35 | 2.884|
| 65-74     | 1821    | 68.99 | 2.74 | 3489 | 68.74 | 2.903| 3744 | 68.47 | 2.671| 2570 | 68.94 | 2.71 |
| 75-84     | 492     | 78.15 | 2.63 | 992  | 77.9 | 2.59 | 1162 | 78.23 | 2.648| 1672 | 78.51 | 2.668|
| 85+       | 72      | 87.76 | 2.93 | 129  | 87.52 | 2.447| 154  | 87.84 | 3.289| 267  | 87.49 | 2.8 |
| Total     | 20177   |    | 43.79 | 17.27| 28968| 47.22 | 17.047| 30519| 46.22 | 17.68| 38701| 46.83 | 18.095|

Discussion

Study results show a highly significant age-independent decline in total testosterone serum levels over the years 2006–2019 for a large population of Israeli patients referred for the first time for a testosterone blood test. These results are in accordance with previous studies which showed a secular decline in testosterone serum levels in earlier years (1970's to 2000's) in other countries (Table 2).
In this analysis we did not adjust for BMI, as this is unclear whether BMI is a potential mediator or confounder since BMI has not been established as a sole explaining parameter in previous studies on longitudinal trends of testosterone. Analysis performed on the research population with available data on BMI showed little variation (< 1 kg/m²) in the mean age-specific BMI between study periods, with no discernible trend (data not shown). We therefore suggest that the observed testosterone decline is not likely to be explained.
by obesity trends.

In two of the previous observational reports (2, 4) adjustment to body mass index (BMI) led to a nullification of the period-related changes in testosterone. However, in the other two observational reports (1, 3) the age-specific testosterone decline remained significant after adjustment to BMI. Additionally, an US longitudinal study (9) of 991 men have shown that a between the years 1982–2002 testosterone decreased more than expected by aging. Decline was evident also in men who did not gain weight during the study. Thus, it cannot be concluded based on previous studies that the secular testosterone decline can be explained by a concurrent secular increase in body weight.

All the patients observed in this study were referred to a testosterone blood test by a physician while the indication for the referral was not available in study. While this is an obvious limitation of the study, particularly of its external validity, there is no reason to believe it affect internal validity, as the indications for the test have not been changed through the observation period. However, there still may be a concern that the observed trend can be explained by a growth in the size of the subpopulation of referred patients that end up having a below-norm level of testosterone in the serum, i.e. that the trend is due to a growth in the number of patients with a discernible problem rather than a decline of testosterone levels in the general healthy population. In order to address this concern, we repeated the analysis only for the samples which were within the normal range with similar results (data not shown).

It should also be noted regarding the external validity that the particularly large sample size in this study leads us to believe that in spite the aforementioned limitation the results can still be reasonably generalized to the general population, especially as most patients referred to this test eventually are not diagnosed with a discernible medical problem affecting the level of testosterone in the serum. Moreover, the age-specific levels of
circulating testosterone are comparable with previous reports, including a study on 58,162 consecutive results in men from a single large pathology laboratory in Australia(10).

Conclusions

The results of this large real-world data analysis corroborate previous scattered reports that mean testosterone for men in developed countries is decreasing is unlikely to be explained by increasing rates of obesity. The biological mechanisms of this disquieting secular trend should be further examined.

Abbreviations

BMI- body mass index

Declarations

Ethics approval and consent to participate

The study protocol has been approved by Maccabi healthcare Services institutional review board. Consent was waived by Maccabi healthcare Services institutional review board.

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to privacy regulations but are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' contributions
Both authors (SE and GC) analyzed and interpreted the study data and had a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures
Figure 1

Trend of testosterone serum levels per age between 2006-2019. (A) Mean total testosterone in serum (nanomole/liter) for patients in a given age for the years 2006-2019 grouped to four year-groups, error bars show standard deviation of the mean. (B) Serum total testosterone values (nanomole/liter) distributions within three age groups over the years.
