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# LIFETIME EXERCISE IS ASSOCIATED WITH EUGONADISM IN AGING MEN: A PRELIMINARY INVESTIGATION

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**Abstract:**

Testosterone is an important biological hormone, which displays a gradual decline with advancing age. Exercise training has been proposed as a first-line therapy for biochemical hypogonadism (clinically low serum testosterone). As such, the present investigation compared the incidence of biochemical hypogonadism (total testosterone  $<11.3 \text{ nmol}\cdot\text{L}^{-1}$ ) in a cohort of otherwise healthy lifelong sedentary men (SED [N=24],  $63\pm 5$  years), compared with a positive control group of lifelong exercisers (LEX [N=16],  $60\pm 5$  years) using electrochemiluminescent immunoassay. Fisher's exact test identified significantly more of the SED group were classified as biochemically hypogonadal than the LEX group (8/24 compared to 2/16 respectively;  $p<.05$ ). These data provide preliminary evidence that exercise may protect against the development of low testosterone defined hypogonadism in aging men.

**Key words:** aging, androgen, eugonadism, exercise, hypogonadism, testosterone

## **Introduction**

The age related decline in circulating testosterone (T) in men is well described (Harman, Metter, Tobin, Pearson & Blackman, 2001; Travison, Araujo, O'Donnell, Kupelian & McKinlay, 2007). Harman et al. (2001) suggested that using total T (TT) criteria, incidence of clinically low T (biochemical hypogonadism) was approximately 20% in men over 60, 30% in men over 70, and 50% in men over 80 yr of age. More recently, the European Male Aging Study (EMAS) estimated more conservatively that 0.1% men aged 40-49 yr, and 5.1% aged 70-79 yr exhibited biochemical hypogonadism (Wu et al., 2010). These figures, considered with a world health organisation (WHO) estimation that more than 2 billion of the world's population will be over 60 years of age by 2050, and a population-level decline in T, independent of aging (Travison et al., 2007) support the contention that incidence of biochemical hypogonadism will escalate in the coming years. Hypogonadism causes a wide range of signs and symptoms including loss of libido, erectile dysfunction, diminished cognitive function, depression, lethargy, osteoporosis, and loss of muscle mass and strength (Petak, Nankin, Spark, Swerdloff & Rodriguez-Rigau, 2002).

There is a pervasive belief that physical exercise can maintain virility by attenuating the age-associated decline in T (Arazi, Damirchi & Asadi, 2013). However, there are few epidemiological and even fewer experimental data to corroborate this tenet. Whilst some reports suggest that 'exceptionally healthy' men do not experience as rapid a decline in serum T compared to unhealthy counterparts (Sparrow, Bosse & Rowe, 1980), this is not always the case (Hayes, et al., 2015a; Cardarelli et al., 2014). For example, Cardarelli et al. (2014) observed that free T was significantly associated with age, diet, diabetes, and hypertension, but not with exercise, obesity, or dyslipidaemia in a group of aging men. Tajar et al. (2012) observed that in a large cohort of aging men (40–79 yrs), hypogonadic individuals had lower muscle mass, bone mineral density, and poorer general health and physical function. Recent

experimental data from our laboratory provides supportive evidence lifelong exercise exerts a positive influence on body composition (Hayes et al., 2013a), cardiorespiratory fitness (Hayes et al., 2013b; 2015a), endothelial function (Grace et al., 2015), and quality of life (Knowles, Herbert, Easton, Sculthorpe & Grace, 2015) in older males. However, the influence of exercise training history on androgen deficiency in aging men is poorly understood. We recently reported TT, free T, and bioavailable T were not different between lifelong exercisers and otherwise healthy, sedentary older males (Hayes et al., 2015a).

Whilst there is some epidemiological and cross-sectional evidence that TT concentrations are associated with improved general health and physical functioning (Aguirre et al., 2014; Tajar et al., 2012), there is limited evidence to support the contention that increased habitual exercise increases TT. As such, the aim of this preliminary study was to determine whether lifelong exercise was associated with reduced incidence of biochemical hypogonadism ( $TT < 11.3 \text{ nmol}\cdot\text{L}^{-1}$ ; Harman et al., 2001) in older males. We hypothesized that lifelong exercise would be associated with biochemical eugonadism, compared with an age-matched cohort of otherwise healthy sedentary males.

## **Materials and methods**

### **Participants**

Prior to experimental data collection, participants were fully habituated and familiarized with procedures to minimize learning effect. Participants provided written informed consent prior to the study which was approved by the University of the West of Scotland Ethics Committee and procedures were in accordance with the Helsinki Declaration of 1975, as revised in 1983. Twenty four otherwise healthy, sedentary males (SED;  $63 \pm 5$

years of age, with a stature of  $175\pm 6$  cm, body mass of  $91\pm 16$  kg, and body mass index [BMI] of  $30\pm 5 \frac{\text{kg}}{\text{m}^2}$ ) and sixteen lifelong exercising males (LEX;  $60\pm 5$  years of age, with a stature of  $174\pm 6$  cm, body mass of  $79\pm 10$  kg, and BMI of  $26\pm 3 \frac{\text{kg}}{\text{m}^2}$ ) participated. Participants recruited for the SED group were not part of an organized exercise program and did not meet the ACSM minimum guidelines for aerobic exercise (Nelson et al., 2007). Participants recruited for the SED group did not participate in any organized exercise and had not done so for  $>30$  years. The LEX group were highly active exercisers and had been so for the previous  $>30$  years. They consisted primarily of current masters' competitors in sports including water-polo, triathlon, sprint cycling, road cycling, and distance running. The non-competitive LEX participants ( $N=7$ ) were highly active cross-trainers and exercise enthusiasts. LEX group status was confirmed by self-reported exercise time and affirmed by differences in  $\text{VO}_{2\text{peak}}$ . LEX recorded their weekly exercise, which included type, frequency, intensity (recorded by heart rate telemetry), and duration of training. Time spent in low to medium intensity ( $<65\%$  heart rate reserve [HRR]), and high-intensity ( $>65\%$  HRR) training totalled  $214\pm 131 \text{ min}\cdot\text{wk}^{-1}$  and  $67\pm 52 \text{ min}\cdot\text{wk}^{-1}$  respectively in LEX.

#### Experimental procedures

Blood samples from each participant were collected 07:00-09:00 h by the same investigator from an antecubital forearm vein following an overnight fast and 20 min supine rest, using a 20-gauge disposable needle equipped with a Vacutainer tube holder (Becton Dickinson, Oxford, UK). Approximately 20 ml of blood was withdrawn and placed in two 10 ml serum tubes. Blood samples were allowed to clot at room temperature prior to being centrifuged at 6,000 rpm at  $15^\circ\text{C}$  for 15 min. Resultant serum was divided into appropriate aliquots and stored at  $-80^\circ\text{C}$  until subsequent analysis by electrochemiluminescence

immunoassay on the E601 module of the Roche Cobas 6000 (Burgess Hill, West Sussex, U.K.). The inter-assay coefficient of variation (CV) over a 6-month period was 4.5%. Analyses were carried out in the Clinical Biochemistry Laboratory at Royal Glamorgan Hospital (Wales, UK).

Stature was measured to the nearest 0.1 cm using a stadiometer (Seca, Birmingham, UK). A multi frequency bioelectrical impedance analyzer (BIA [Tanita MC-180MA Body Composition Analyzer, Tanita UK Ltd.]) was used to determine body composition.

Peak aerobic capacity was determined using a Cortex II Metalyser 3B-R2 (Cortex, Biophysik, Leipzig, Germany) as previously described (Grace et al., 2015; Hayes et al., 2015b) using a modified Storer test (Storer, Davis, & Caiozzo, 1990).

#### Statistical analysis

Data were analyzed using SPSS (version 21.0; IBM North America, New York, NY, USA). Parametric assumptions were checked with the use of numerical methods; checking studentized residual, Shapiro-Wilk test and Mauchly's Test of sphericity. Paired samples student's t-test was used to determine whether participant characteristics were significantly different between groups. Fisher's exact test was used to test whether SED contained more biochemically hypogonadal individuals ( $TT < 11.3 \text{ nmol}\cdot\text{L}^{-1}$ ) than LEX. Significance was set a priori at  $p < .05$  and data are presented as mean  $\pm$  standard deviation (SD).

## Results

Whilst there was no significant difference in TT between groups ( $14.8 \pm 3.7$  and  $13.3 \pm 6.2$  nmol·L<sup>-1</sup> in LEX and SED respectively), Fischer's exact test indicated more SED participants were biochemically hypogonadal than LEX participants (8/24 compared to 2/16 respectively;  $p=0.046$  [Figure. 1]). As displayed in Table 1, LEX has significantly greater  $VO_{2peak}$ , lower total body mass and body fat percentage compared to SED ( $p < 0.01$  in all instances).

**\*\*\*INSERT TABLE 1 NEAR HERE \*\*\***

**\*\*\*INSERT FIGURE 1 NEAR HERE\*\*\***

## **Discussion**

The main finding of the present investigation was that lifelong sedentariness is associated with greater incidence of biochemical hypogonadism than lifelong exercise. To the authors' knowledge, this is the first investigation to determine the effect of lifelong exercise on the incidence of biochemical hypogonadism. These data provide preliminary evidence that lifelong exercise may protect against biochemical hypogonadism. A caveat to this however, is that lifelong exercise may not be protective, but rather individuals who preserve eugonadism are capable of maintaining lifelong exercise habits and that LEX is a self-selecting group. Given that there was no difference in mean TT between groups, this work highlights the importance of including incidence of hypogonadism within cohorts, rather than merely a comparison of means in future investigations.

In the absence of similar studies in humans, androgen-related studies conducted in the rodent model offers some useful mechanistic direction. For instance, Dubois and colleagues (2015) investigated the influence of androgen deficiency in a group of orchidectomized mice.



These authors reported that orchidectomized mice had a lower body mass at 10 weeks, but gained more total body mass and fat mass when fed a high fat diet, compared to sham mice. As observed by Dubois et al. (2015), as well as previous rodent investigations (Rana, Fam, Clarke, Pang & Zajac, 2011), androgen deficiency is associated with reduced voluntary ambulatory activity. Whilst caution must be exerted extrapolating rodent data to human behavior, the findings of the present investigation may, in part, support the findings of Dubois et al. (2015) in suggesting humans with biochemical hypogonadism may engage in less exercise. However, deciphering causality in the relationship between biochemical hypogonadism and exercise is difficult (i.e. does biochemical hypogonadism precede reduced exercise, or does reduced exercise cause biochemical hypogonadism?). We propose that more longitudinal studies are required to elucidate whether there is a causal relationship between exercise and eugonadism, or between sedentariness and hypogonadism.

In conclusion, the present data provide novel and preliminary associative evidence that lifelong exercise preserves biochemical eugonadism in older men, compared with age-matched lifelong sedentary counterparts. Future research may wish to concern whether lifelong exercise is causal in protecting TT or if lifelong exercisers represent a self-selecting eugonadal group. Moreover, it may be of interest if to determine whether sedentary biochemically hypogonadal men adhere to, and adapt to, exercise training in a similar manner to sedentary eugonadal men.

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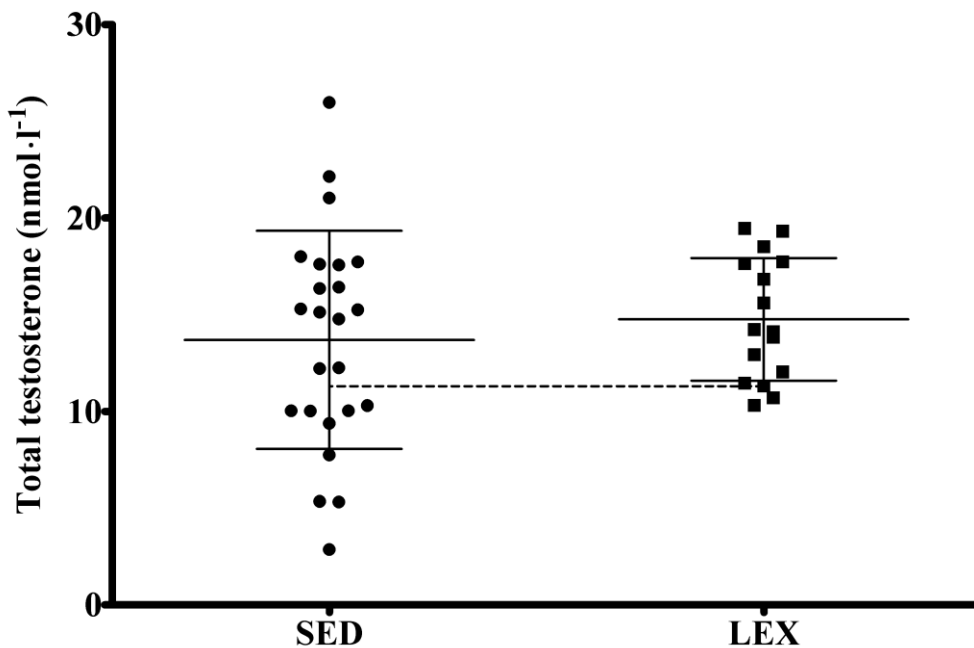
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**Table. 1** Participant characteristics of lifelong sedentary (SED) and lifelong exercising (LEX) aging males.  $VO_{2peak}$ =peak aerobic capacity. Data are presented as mean $\pm$ SD.

Variable	SED (N=24)	LEX (N=16)
Age (years)	63 $\pm$ 5	60 $\pm$ 5
Stature (cm)	175 $\pm$ 6	174 $\pm$ 6
Mass (kg)	91 $\pm$ 16*	79 $\pm$ 10
BMI ( $\frac{kg}{m^2}$ )	30 $\pm$ 5*	26 $\pm$ 3
Lean mass (kg)	63.8 $\pm$ 8.7	62.8 $\pm$ 5.9
Body fat percentage (%)	28.7 $\pm$ 5.0*	19.7 $\pm$ 6.6
$VO_{2peak}$ ( $ml \cdot kg \cdot min^{-1}$ )	26.9 $\pm$ 5.3*	40.0 $\pm$ 5.7

\*Denotes significant differences from LEX group ( $p < 0.01$ ).



**Fig. 1** Total testosterone in a group of lifelong sedentary (SED) and lifelong exercising (LEX) aging males. Individual data points and mean  $\pm$  SD are shown displayed. The threshold for biochemical hypogonadism ( $11.3 \text{ nmol} \cdot \text{L}^{-1}$ ) has been marked as a dashed line.