Endocrine
DOI 10.1007/s12020-015-0771-y

RESEARCH LETTER

Pre-training levels of testosterone and sex hormone-binding globulin are not correlated with training adaptations in fat mass and insulin sensitivity in healthy young men

Thine Hvid[1] · Thorbjorn Akerstrom[1] · Søren Nielsen[1] · Christina Yfanti[1] · Anders Juul[2] · Birgitte Lindegaard[1] · Bente K. Pedersen[1] · Pernille Hojman[1]

Received: 24 May 2015 / Accepted: 6 October 2015

Introduction

The male sex hormone testosterone influences muscle growth and strength, body composition and insulin sensitivity. These factors are also regulated by exercise, but whether pre-training levels of circulating testosterone are associated with exercise-induced adaptations in fat mass (FM) and insulin sensitivity is unknown. Studies in healthy young men suggest that endurance training induces greater reductions in body weight and FM in subjects with the highest baseline levels of testosterone [1]. Yet, endurance training may also change plasma total testosterone (TT) and sex hormone-binding globulin (SHBG) levels [2], and changes in these hormone concentrations may correlate inversely with changes in FM and visceral adipose tissue in response to endurance training [1, 3, 4]. However, not all studies find such associations [4, 5]. While these studies imply that pre-exercise levels of TT could be a modulating factor for FM in response to endurance training, such correlations between pre-exercise levels of TT and insulin sensitivity have not been investigated. Thus, we aimed to determine whether pre-training levels of TT and SHBG are related to endurance training-induced improvements in body adiposity and insulin sensitivity in healthy young men.

✉ Pernille Hojman
phojman@inflammation-metabolism.dk

[1] Department of Infectious Disease, Centre of Physical Activity Research, The Centre of Inflammation and Metabolism, Rigshospitalet 7641, Blegdamsvej 9, 2100 Copenhagen, Denmark

[2] Department of Growth and Reproduction 6 EDMaRC, Faculty of Health and Medical Sciences, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Methods

Thirty-one healthy young men were included in the training study. Results from this training study have previously been reported [6–10]. The study was approved by the Copenhagen and Frederiksberg Ethics Committee, Denmark (KF 01 289, 434), and performed according to the declaration of Helsinki. Exclusion criteria included regular physical exercise more than two times per week, BMI >30 kg/m^2, smoking, impaired glucose tolerance and use of medication. The subjects were initially randomised to placebo ($n = 10$), antioxidant supplementation consisting of 500 mg of vitamin C and 400 IU of vitamin E daily for 16 weeks, starting 4 weeks before onset of the training ($n = 11$) [7] or glucose supplementation consisting of 1.0 g/(kg h) during all training sessions ($n = 10$). No differences were observed between these groups in metabolic parameters, body composition, TT or SHBG in response to any of the interventions. Thus, the three groups were pooled ($n = 31$). The training protocol comprised of alternating interval (75–91 % P_{max} with durations of 60–80 min) and continuous (55–66 % P_{max} with durations of 85–155 min) cycling training sessions five times/week for 12 weeks with P_{max} being determined every Monday to ensure training progression. The full exercise protocol is described in [8]. Blood samples were collected after an overnight fast both before ($n = 31$) and after the training period ($n = 25$). One person in the glucose supplementation group was missing in the pre-samples compared to previous publications (originally $n = 32$), and seven samples equally distributed among the groups were missing after the training intervention. Serum levels of TT and SHBG were measured by time-resolved fluoroimmunoassays (DELFIA) with a detection limit of 0.23 nmol/l for both. Intra- and inter-assay coefficients of

Published online: 19 October 2015

Table 1 Correlation analyses between total testosterone, SHBG or total testosterone/SHBG and measures of body mass, insulin sensitivity and fitness

	Total testosterone (pre)		SHBG (pre)		Total testosterone/SHBG (pre)	
	r	*p* value	*r*	*p* value	*r*	*p* value
BMI						
Pre	−0.43	**<0.05**	−0.49	**<0.01**	0.27	>0.2
Delta	0.22	>0.2	−0.053	>0.2	0.16	>0.2
Fat mass						
Pre	−0.48	**<0.01**	−0.50	**<0.01**	0.31	>0.2
Delta	0.088	>0.2	−0.099	>0.2	0.038	>0.2
Trunk fat mass						
Pre	−0.47	**<0.01**	−0.55	**<0.01**	0.37	0.052
Delta	0.20	>0.2	0.039	>0.2	−0.057	>0.2
GIR						
Pre	0.18	>0.2	0.43	**<0.05**	−0.37	**<0.05**
Delta	0.14	>0.2	0.23	>0.2	−0.17	>0.2
HOMA						
Pre	−0.27	>0.2	−0.38	**<0.05**	0.26	>0.2
Delta	0.099	>0.2	0.19	>0.2	−0.10	>0.2
VO_2 max						
Pre	0.31	>0.2	0.54	**<0.01**	−0.44	**<0.05**
Delta	−0.073	>0.2	0.046	>0.2	−0.063	>0.2
Lean body mass						
Pre	0.016	>0.2	0.050	>0.2	−0.10	>0.2
Delta	0.22	>0.2	0.057	>0.2	0.22	>0.2
	Total testosterone (post)		SHBG (post)		Total testosterone/SHBG (post)	
	r	*p* value	*r*	*p* value	*r*	*p* value
BMI						
Post	−0.23	>0.2	−0.40	**<0.05**	0.26	>0.2
Fat mass						
Post	−0.41	**<0.05**	−0.51	**<0.01**	0.22	>0.2
Trunk fat mass						
Post	−0.41	**<0.05**	−0.54	**<0.01**	0.29	>0.2
GIR						
Post	0.25	>0.2	0.34	0.07	−0.38	0.058
HOMA						
Post	−0.13	>0.2	−0.32	>0.2	0.28	>0.2
VO_2 max						
Post	0.46	**<0.05**	0.33	0.085	−0.14	>0.2
Lean body mass						
Post	0.23	>0.2	0.21	>0.2	0.15	>0.2

Data were analyzed with GraphPad Prism 6. All data were tested for normality of distribution using the Kolmogorov–Smirnov test and were log-transformed to achieve an approximate normal distribution when necessary. Associations between parameters were tested by Spearman correlation coefficients. *p* values <0.05 were considered statistically significant and are depicted in bold

variation (CV) were less than 12 % for TT and less than 6 % for SHBG. Body composition was determined by DXA scans, and insulin sensitivity was measured as glucose infusion rates (GIR) during a euglycemia (5 mM)-hyperinsulinemic clamp [7]. Normal distribution was tested by Kolmogorov–Smirnov test and log-transformed if necessary. Associations between parameters ($n = 31$ for baseline testing) and ($n = 25$ for post-training testing) were tested by linear regression analysis with Spearman correlation coefficients.

Results

The subjects were 21–39 years ($n = 31$), non-obese with a mean BMI of 25.1 ± 2.7 kg/m^2 and mean VO_2 max was 50.5 ± 7.6 ml(O_2)/(min kg). TT and SHBG levels were 9.37–23.60 and 15.0–52.0 nmol/l, respectively. One subject was hypogonadal (testosterone <10.4 nmol/l). Twelve weeks of endurance training did not change TT or SHBG concentration, but increased VO_2 max by 21.3 ± 10.9 % ($p < 0.01$), reduced whole-body FM by 3.3 ± 2.7 kg ($p < 0.01$), lowered trunk FM by 2.0 ± 1.7 kg ($p < 0.01$) and increased lean body mass by 1.2 ± 1.4 kg ($p < 0.01$). The GIR during the euglycemic hyperinsulinemic clamps increased by 20.1 ± 23.4 % ($p < 0.01$) after 12 weeks of endurance training.

TT correlated inversely with BMI, FM and trunk FM before the training period ($r = -0.43$, $p < 0.05$, $r = -0.48$, $p < 0.01$ and $r = -0.47$, $p < 0.01$, Table 1) and with FM and trunk FM after training ($r = -0.41$ and $r = -0.41$ m both $p < 0.05$, Table 1). Similarly, SHBG levels were inversely correlated with BMI, FM and trunk FM before training ($r = -0.49$, $r = -0.50$ and $r = -0.55$; all $p < 0.01$) and after training (Table 1). The ratio between TT and SHBG did not correlate with BMI, FM or trunk FM neither before nor after training. Pre-training levels of TT and SHBG were not associated with exercise-induced changes in BMI, FM or trunk FM.

TT did not at any time correlate with insulin sensitivity, whereas SHBG was positively correlated with insulin sensitivity before ($r = 0.43$; $p < 0.05$) but not after ($r = 0.34$; $p = 0.07$) training. Of note, the ratio between TT and SHBG correlated with GIR before ($r = -0.37$; $p < 0.05$) and after ($r = -0.38$; $p = 0.058$) training. Pre-training levels of TT, SHBG and the ratio between the two were not associated with training-induced changes in insulin sensitivity.

SHBG and the ratio TT/SHBG correlated with VO_2 max before training ($r = 0.47$, $p < 0.01$, $r = -0.44$, $p < 0.05$, respectively). TT correlated with VO_2 max after training ($r = 0.46$, $p < 0.05$). Pre-training levels of TT and SHBG were not correlated to changes in VO_2 max across the training period. Neither TT nor SHBG were associated with fat-free mass before or after training.

Discussion

Here we show that pre-training levels TT and SHBG levels do not correlate with training-induced improvements in FM and insulin sensitivity in non-obese young healthy men. However, SHBG was associated with insulin sensitivity before training. In line with previous studies, we found that pre-training levels of TT and SHBG are associated with measures of FM [11–13]. As TT did not change during the exercise intervention, no correlations between changes in TT and other physiological adaptations were performed. The high-intensity endurance training regime induced remarkable increases in VO_2 max and insulin sensitivity, which was accompanied by 3.3 kg reduction in FM and 2.0 kg reduction in trunk FM. As pre-exercise levels of TT and SHBG were not associated with these changes, our findings suggest that young healthy men are not more susceptible to endurance training-induced changes in insulin sensitivity or body adiposity regardless of their pre-training TT levels.

Low levels of TT is a risk factor for metabolic syndrome and type 2 diabetes [14, 15], even in men under the age of 40 [16]. The predictive role of testosterone is thought mainly to occur through its association with insulin sensitivity and FM [16]. Thus, the ability to reduce FM and increase insulin sensitivity despite low pre-training levels of TT might be of clinical importance.

In conclusion, we show that pre-training levels of TT and SHBG are not associated with exercise-induced adaptations in FM and insulin resistance. These results give promise for prostate cancer patients, where training can be exploited to reduce therapy-related adverse metabolic effects, despite their treatment-related hypogonadism.

Acknowledgments Ruth Rousing, Hanne Villumsen and Kirsten Jørgensen are acknowledged for their technical assistance.

Funding The Centre of Inflammation and Metabolism (CIM) is supported by a grant from the Danish National Research Foundation (DNRF55). The Centre for Physical Activity Research (CFAS) is supported by a grant from Trygfonden. The Copenhagen Muscle Research Centre (CMRC) is supported by a grant from the Capital Region of Denmark.

Compliance with ethical standards

Conflict of Interest The authors have no conflict of interest, financial or otherwise, to declare.

References

1. J. Pritchard, J.P. Despres, J. Gagnon, A. Tchernof, A. Nadeau, A. Tremblay, C. Bouchard, Plasma adrenal, gonadal, and conjugated steroids following long-term exercise-induced negative energy balance in identical twins. Metabolism **48**, 1120–1127 (1999)
2. A.C. Hackney, Effects of endurance exercise on the reproductive system of men: the "exercise-hypogonadal male condition". J. Endocrinol. Invest. **31**, 932–938 (2008)
3. J.A. Hounard, C. McCulley, M.H. Shinebarger, N.J. Bruno, Effects of exercise training on plasma androgens in men. Horm. Metab. Res. **26**, 297–300 (1994)
4. V.N. Hawkins, K. Foster-schubert, J. Chubak, B. Sorensen, C.M. Ulrich, F.Z. Stancyzk, S. Plymate, J. Stanford, E. White, J.D. Potter, A. McTiernan, Effect of exercise on serum sex hormones

in men: a 12-month randomized clinical trial. Med. Sci. Sports Exerc. **40**, 223–233 (2008)
5. G.D. Wheeler, M. Singh, W.D. Pierce, W.F. Epling, D.C. Cumming, Endurance training decreases serum testosterone levels in men without change in luteinizing hormone pulsatile release. J. Clin. Endocrinol. Metab. **72**, 422–425 (1991)
6. A. Rinnov, C. Yfanti, S. Nielsen, T. Akerström, L. Peijs, A. Zankari, C.P. Fischer, B.K. Pedersen, Endurance training enhances skeletal muscle interleukin-15 in human male subjects. Endocrine **45**, 271–278 (2014)
7. C. Yfanti, A.R. Nielsen, T. Akerström, S. Nielsen, A. Rose, E.A. Richter, J. Lykkesfeldt, C.P. Fischer, B.K. Pedersen, Effect of antioxidant supplementation on insulin sensitivity in response to endurance exercise training. Am. J. Physiol. Endocrinol. Metab. **300**, E761–E770 (2011)
8. C. Yfanti, T. Akerström, S. Nielsen, A.R. Nielsen, R. Mounier, O.H. Mortensen, J. Lykkesfeldt, A. Rose, C.P. Fischer, B.K. Pedersen, Antioxidant supplementation does not alter endurance training adaptation. Med. Sci. Sports Exerc. **42**, 1388–1395 (2010)
9. S. Nielsen, C. Scheele, C. Yfanti, T. Akerström, A.R. Nielsen, B.K. Pedersen, M.J. Laye, Muscle specific microRNAs are regulated by endurance exercise in human skeletal muscle. J. Physiol. **588**, 4029–4037 (2010)
10. C. Yfanti, C.P. Fischer, S. Nielsen, T. Akerström, A.R. Nielsen, A.S. Veskoukis, D. Kouretas, J. Lykkesfeldt, H. Pilegaard, B.K. Pedersen, Role of vitamin C and E supplementation on IL-6 in response to training. J. Appl. Physiol. **112**, 990–1000 (2012)
11. D.M. Greenfield, S.J. Walters, R.E. Coleman, B.W. Hancock, R. Eastell, H.A. Davies, J.A. Snowden, S.M. Derogatis, S.M. Shalet, R.J. Ross, Prevalence and consequences of androgen deficiency in young male cancer survivors in a controlled cross-sectional study. J. Clin. Endocrinol. Metab. **92**, 3476–3482 (2007)
12. T.L. Nielsen, C. Hagen, K. Wraae, K. Brixen, P.H. Petersen, E. Haug, R. Larsen, M. Andersen, Visceral and subcutaneous adipose tissue assessed by magnetic resonance imaging in relation to circulating androgens, sex hormone-binding globulin, and luteinizing hormone in young men. J. Clin. Endocrinol. Metab. **92**, 2696–2705 (2007)
13. A. Tchernof, J.P. Despres, A. Dupont, A. Belanger, A. Nadeau, S. Prud'homme, S. Moorjani, P.J. Lupien, F. Labrie, Relation of steroid hormones to glucose tolerance and plasma insulin levels in men. Importance of visceral adipose tissue. Diabetes Care **18**, 292–299 (1995)
14. M. Grossmann, E.J. Gianatti, J.D. Zajac, Testosterone and type 2 diabetes. Curr. Opin. Endocrinol. Diabetes Obes. **17**, 247–256 (2010)
15. D.E. Laaksonen, L. Niskanen, K. Punnonen, K. Nyyssönen, T.P. Tuomainen, V.P. Valkonen, R. Salonen, J.T. Salonen, Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care **27**, 1036–1041 (2004)
16. R. Haring, H. Völzke, S.B. Felix, S. Schipf, M. Dörr, D. Rosskopf, M. Nauck, C. Schöfl, H. Wallaschofski, Prediction of metabolic syndrome by low serum testosterone levels in men: results from the study of health in Pomerania. Diabetes **58**, 2027–2031 (2009)