Endurance training improves insulin sensitivity and body composition in prostate cancer patients treated with androgen deprivation therapy

Thine Hvid¹, Kamilla Winding¹, Anders Rinnov¹, Thomas Dejgaard¹, Carsten Thomsen², Peter Iversen³, Klaus Brasso³, Kari J Mikines⁴, Gerrit van Hall^{1,5}, Birgitte Lindegaard¹, Thomas P J Solomon¹ and Bente K Pedersen¹

¹The Centre of Inflammation and Metabolism, Department of Infectious Diseases and Copenhagen Muscle Research Centre, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

²Department of Diagnostic Radiology, Rigshospitalet, Copenhagen, Denmark

³Department of Urology, Rigshospitalet, Copenhagen, Denmark

⁴Department of Urology, Herlev University Hospital, Copenhagen, Denmark

⁵The Metabolic Mass Spectrometry Facility, Rigshospitalet, Copenhagen, Denmark

Correspondence should be addressed to T Hvid

Email
thvid@inflammation-metabolism.dk

Abstract

Insulin resistance and changes in body composition are side effects of androgen deprivation therapy (ADT) given to prostate cancer patients. The present study investigated whether endurance training improves insulin sensitivity and body composition in ADT-treated prostate cancer patients. Nine men undergoing ADT for prostate cancer and ten healthy men with normal testosterone levels underwent 12 weeks of endurance training. Primary endpoints were insulin sensitivity (euglycemic–hyperinsulinemic clamps with concomitant glucose-tracer infusion) and body composition (dual-energy X-ray absorptiometry and magnetic resonance imaging). The secondary endpoint was systemic inflammation. Statistical analysis was carried out using two-way ANOVA. Endurance training increased $\text{VO}_{2\text{max}}$ ($\text{ml}(\text{O}_2)/\text{min per kg}$) by 11 and 13% in the patients and controls respectively ($P < 0.0001$). The patients and controls demonstrated an increase in peripheral tissue insulin sensitivity of 14 and 11% respectively ($P < 0.05$), with no effect on hepatic insulin sensitivity ($P = 0.32$). Muscle protein content of GLUT4 (SLC2A4) and total AKT (AKT1) was also increased in response to the training ($P < 0.05$ and $P < 0.01$ respectively). Body weight ($P < 0.0001$) and whole-body fat mass (FM) ($P < 0.01$) were reduced, while lean body mass ($P = 0.99$) was unchanged. Additionally, reductions were observed in abdominal ($P < 0.01$), subcutaneous ($P < 0.05$), and visceral ($P < 0.01$) FM amounts. The concentrations of plasma markers of systemic inflammation were unchanged in response to the training. No group $\times$ time interactions were observed, except for thigh intermuscular adipose tissue (IMAT) ($P = 0.01$), reflecting a significant reduction in the amount of IMAT in the controls ($P < 0.05$) not observed in the patients ($P = 0.64$). In response to endurance training, ADT-treated prostate cancer patients exhibited improved insulin sensitivity and body composition to a similar degree as eugonadal men.

Key Words

- ▶ prostate cancer
- ▶ androgen deprivation therapy
- ▶ endurance training
- ▶ insulin sensitivity and body composition

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Introduction

The cornerstone treatment for men with advanced and metastatic prostate cancer is androgen deprivation therapy (ADT). ADT results in castration levels of serum testosterone that cause delayed tumor progression and, in certain stages of the disease, also improved cancer-specific survival (Sharifi *et al.* 2005). However, ADT also causes metabolic complications such as hyperlipidemia (Smith *et al.* 2002) and insulin resistance (Basaria *et al.* 2006, Smith *et al.* 2006, 2008a, Hamilton *et al.* 2011) and unfavorable changes in body composition such as a loss of lean body mass (LBM; Berruti *et al.* 2002, Smith 2004, Lee *et al.* 2005, Smith *et al.* 2008a,b, Hamilton *et al.* 2011) and a gain in fat mass (FM; Berruti *et al.* 2002, Smith 2004, Boxer *et al.* 2005, Greenspan *et al.* 2005, Lee *et al.* 2005, Smith *et al.* 2008a,b). Increased FM following ADT is particularly pronounced in the abdominal compartment (Braga-Basaria *et al.* 2006) and may reflect an accumulation of both visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) (Smith *et al.* 2002, 2008b, Hamilton *et al.* 2011).

Obesity is associated with a state of low-grade inflammation (Cancello & Clement 2006). The consequence of the ADT-induced increase in total and abdominal FM in prostate cancer patients is, however, controversial regarding inflammation status. Increased systemic concentrations of inflammatory cytokines in ADT-treated prostate cancer patients have been documented, but they may be dependent on ADT duration (Maggio *et al.* 2006, Smith *et al.* 2008a,b, Saylor *et al.* 2012) and whether or not the cancer is castration resistant (Drachenberg *et al.* 1999, Wise *et al.* 2000).

Insulin resistance and abdominal obesity characterize the metabolic syndrome and are risk factors for type 2 diabetes (Lechleitner 2008). Prostate cancer patients managed with ADT have an increased risk of the metabolic syndrome and diabetes compared with patients not receiving ADT and healthy controls (Braga-Basaria *et al.* 2006, Keating *et al.* 2006, Kintzel *et al.* 2008). A growing number of studies have also reported of an increased risk of cardiovascular disease in ADT-treated prostate cancer patients (Faris & Smith 2010). Strategies that prevent the adverse effects of ADT on insulin resistance and body composition seem crucial to decrease the incidence of these obesity-related diseases. Several studies have investigated the effect of strength training alone (Segal *et al.* 2003, Galvao *et al.* 2006, Hansen *et al.* 2009, Alberga *et al.* 2012, Hanson *et al.* 2013) or in combination with light aerobic training (Galvao *et al.* 2010, 2011, Bourke *et al.* 2011). Strength training can prevent the deterioration in

LBM and reduce increases in FM in ADT-treated men with prostate cancer (Alberga *et al.* 2012). In contrast, neither the loss of LBM nor the increase in FM is prevented by endurance training (Alberga *et al.* 2012), suggesting that the lack of testosterone may hinder the beneficial effects of endurance training on body composition. Nevertheless, it remains to be determined whether endurance training alters the regional distribution of adiposity. Visceral adiposity *per se* may be an independent risk factor for the development of insulin resistance, type 2 diabetes, and features of the metabolic syndrome (Fox *et al.* 2007).

Exercise training improves insulin sensitivity (Hawley & Lessard 2008). This effect of training has never been investigated in prostate cancer patients receiving ADT. Exercise also induces anti-inflammatory effects (Mathur & Pedersen 2008). While strength training alone does not improve the inflammation status in ADT-treated prostate cancer patients (Galvao *et al.* 2008), combined aerobic and strength training results in decreased systemic inflammation (Galvao *et al.* 2010), suggestive of an anti-inflammatory effect of endurance training alone in such patients.

The primary aim of this study was to investigate the effect of 12 weeks of supervised endurance training on insulin sensitivity and body composition in ADT-treated prostate cancer patients, with special reference to visceral fat. The secondary aim was to investigate the effect of endurance training on the concentrations of systemic markers of inflammation in this group of patients. To elucidate whether men with testosterone ablation have the same beneficial effects of endurance training as men with normal levels of testosterone, a group of age-matched healthy eugonadal men were also included in the study.

Subjects and methods

Subjects

Prostate cancer patients ($n=10$) receiving LHRH agonist therapy (ADT) for >3 months were enrolled from the Department of Urology, Rigshospitalet, and Department of Urology, Herlev Hospital, to undergo a 3-month exercise training intervention. The patients were receiving LHRH agonist as either 10.8 mg injections of Zoladex (AstraZeneca) every third month or as 50 mg Vastas implants annually (Orion Pharma, Nivå, Denmark). All patients had castration levels of testosterone (<1.7 nmol/l). Control subjects ($n=11$) were healthy males matched by age, BMI, and aerobic fitness with

normal testosterone levels (10.0–28.0 nmol/l). Before inclusion, a medical examination with blood test screening was performed. The purpose of the study, possible risks, and discomforts were explained to the subjects and written consent was obtained. The study was approved by the Ethical Committee of Copenhagen and Frederiksberg (H-4-2009-102) and was performed in accordance with the Declaration of Helsinki. Exclusion criteria included severe cardiovascular disease, severe arthritis, severe neuropathy, severe hypertension, therapy with antidiabetic agents, and exercise training >2 times per week. Due to poor adherence to the training, one subject in each group was excluded from the study. The final study population comprised nine prostate cancer patients and ten control subjects.

Training protocol

The subjects underwent supervised endurance training on a cycle ergometer three times per week for 12 weeks. Heart rate was continuously monitored (RS400; Polar, Kempele, Finland). The participants trained at the heart rate corresponding to the desired percentage of maximal oxygen consumption (VO_{2max}) measured during an incremental workload exercise test (described below). Each training session consisted of 5 min of warm up, 35 min of interval training, and 5 min of cool down. Varying interval programs were used with the intention to keep up motivation and adherence to the training. The training consisted of 5–10-min intervals (55–75% of VO_{2max}) on the first week day of the training, 5–25-min intervals (55–75% of VO_{2max}) on the second day, and 1–5-min intervals (50–100% of VO_{2max}) on the third day. The mean training intensity was targeted at 65% of VO_{2max} in the first 6 weeks and at 75% of VO_{2max} in the last 6 weeks. The subjects were allowed to miss no more than 10% of the training sessions.

Diet and physical activity

The subjects were instructed to maintain their habitual diet and level of physical activity during the study. The subjects completed the diet and activity records for 3 days in the beginning of the training period and for 3 days at the end of the training period. Energy intake and expenditure were determined using the Dankost Sport software (Dansk Catering Center A/S, Copenhagen, Denmark). Complete registration was, however, only provided for 11 subjects. Diet was also registered 2 days before the pre-intervention clamp, and the subjects were

instructed to ingest the same diet 2 days before the post-intervention clamp. The subjects were requested not to perform any strenuous physical activity 2 days before the clamp measurements and oral glucose tolerance test (OGTT).

Maximal oxygen consumption (VO_{2max}) test

Prior to the study, the subjects underwent an incremental exercise test to volitional fatigue on a cadence independent cycle ergometer. Oxygen consumption (VO_2) was measured by indirect calorimetry (Quark b2; CosMed, Rome, Italy). VO_{2max} was considered obtained when two of the following three criteria were achieved: i) respiratory exchange ratio ≥ 1.10 ; ii) VO_2 reached a plateau; and iii) cycling cadence <60 r.p.m. for more than 10 s. Heart rate was recorded continuously during the test. The VO_{2max} test was repeated after 6 weeks of training to adjust the absolute workload and following the 12 weeks of training.

Oral glucose tolerance test

A standard 2-h OGTT with a glucose load of 75 g was performed following an overnight fast and pre and post training. The post-exercise OGTT was performed 48–96 h after the last exercise bout. Blood samples were collected into glass tubes containing EDTA at –10, –5, 0, 30, 60, 90, and 120 min and were immediately spun at 3500 g for 15 min at 4 °C. Plasma was isolated and stored at –20 °C until analyzed. The area under the curve (AUC) for insulin and glucose was calculated using the trapezoidal rule.

Euglycemic-hyperinsulinemic clamp

A euglycemic-hyperinsulinemic clamp was performed before and after the training period. The subjects reported to the laboratory between 0700 and 0800 h after an overnight fast (12 h) and 46–48 h after the VO_{2max} test both pre and post training. An i.v. catheter was inserted into the antecubital vein of one arm for the infusion of insulin and glucose. For blood sampling, a second catheter was placed into a dorsal hand vein on the contralateral arm. The hand was wrapped in a heating blanket to arterialize venous blood samples. After obtaining baseline blood samples, an i.v. priming dose of 17.6 $\mu\text{mol/kg}$ [6,6- $^2\text{H}_2$]glucose was injected. Later, a 0.4 $\mu\text{mol/min}$ per kg infusion of [6,6- $^2\text{H}_2$]glucose was injected. After 2 h of [6,6- $^2\text{H}_2$]glucose infusion, a 3-h 40 mU/m² per min infusion of insulin (Actrapid; Novo Nordisk, Bagsværd, Denmark) was injected. After 30 min of insulin infusion, the infusion rate of [6,6- $^2\text{H}_2$]glucose was increased to

1.2 $\mu\text{mol}/\text{min}$ per kg. Arterialized plasma glucose concentration was measured every 10 min (EML 105, Radiometer, Brønshøj, Denmark) throughout the clamp, and euglycemia (5.5 mmol/l) was achieved by a variable-rate infusion of 20% (w/v) glucose. Blood samples for the determination of tracer-to-tracee ratio were collected every 10 min during the last 30 min of both the basal and insulin-stimulated states.

Tissue samples

Muscle tissue from m. vastus lateralis was obtained under local anesthesia using the percutaneous needle biopsy method with suction during the basal state on the clamp days. Tissue samples were cleaned free of blood and connective tissue and quickly frozen in liquid nitrogen and stored at -80°C until analyzed.

Body composition

Whole-body fat-free mass, FM, and trunk FM were measured before and after the intervention using dual-energy X-ray absorptiometry (Lunar Prodigy, version 8.8; GE Medical Systems, Madison, WI, USA).

Magnetic resonance (MR) imaging was performed using a 3-Tesla MR scanner (Siemens Magnetom Total imaging matrix magnetic resonance scanner, Erlangen, Germany). Multi-slice images from the top of the femoral head to the upper border of the liver were analyzed using the software program Mango (Multi-Images Analysis GUI). VAT volume was calculated according to the slice thickness and cross-sectional area of each image. SAT volume was calculated by subtracting VAT volume from the total abdominal fat volume. VAT was defined as the amount of fat deposited around the internal organs delineated by the inner wall of the abdominal muscle. SAT was defined as adipose tissue located directly beneath the skin. The right thigh was measured from the femoral head to the tibiofemoral joint line, and the average volume of intermuscular adipose tissue (IMAT) was measured in the middle one-third of the thigh. IMAT was defined as adipose tissue located beneath the fascia and between muscles. All MR analyses were performed by the same investigator in a blinded manner.

Laboratory analysis

Plasma plasminogen activator inhibitor-1 (PAI-1) concentration was measured using ELISA (R&D Systems, Minneapolis, MN, USA), and interleukin 6 (IL6), tumor necrosis

factor α (TNF α (TNF)), adiponectin, and leptin concentrations were measured using ELISA (Meso Scale Discovery, Gaithersburg, MD, USA). All samples were run as duplicates and mean concentrations were calculated. Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, testosterone, prostate-specific antigen (PSA), glucose, and insulin concentrations were measured using local routine laboratory methods.

Muscle biopsies were prepared for homogenization using a lysis buffer (50 mM Tris-HCl, 150 mM NaCl, 1 mM EDTA, 1 mM EGTA, 50 mM sodium fluoride, and 5 mM sodium pyrophosphate) and homogenized using Tissue-Lyser (Qiagen). The concentrations of the muscle lysates were measured using the Bradford assay (Bio-Rad Protein Assay, #500-0006), and muscle lysates were separated on TGX 4–14% gel (Bio-Rad) and transferred onto PVDF membranes (Life Technologies) before incubation with the appropriate antibodies. The primary antibodies used were total AKT (no. 9272, Cell Signalling Technology, Danvers, MA, USA) and glucose transporter 4 (GLUT4) (Thermo Scientific, Slangerup, Denmark). The secondary antibodies used were anti-rabbit HRP (no. 7074, Cell Signalling Technology) for AKT (AKT1) and anti-rabbit HRP (P0448, Dako, Glostrup, Denmark) for GLUT4 (SLC2A4). The intensities of the protein bands were detected using Image Lab 3.0 (Bio-Rad) and normalized to the intensity of the Reactive Brown (RB) total protein stain. Results are reported in arbitrary units.

Glucose kinetics calculations

Enrichment of plasma glucose was determined as described previously (Plomgaard *et al.* 2005) using liquid chromatography–mass spectrometry (Finnegan aQa). The rate of appearance (R_a) and rate of disappearance (R_d) of glucose were determined in the basal state and during the last 30 min of the clamp, where a steady state of glucose infusion and glucose concentration was achieved, using the steady-state single pool model of Steele (Steele 1959). Hepatic insulin sensitivity was estimated as the difference between total R_a and exogenous glucose infusion rate during the steady-state hyperinsulinemia. Peripheral tissue insulin sensitivity was estimated as R_d during the steady-state hyperinsulinemia.

Statistical analysis

Data were analyzed using SAS 9.1.3 (SAS Institute, Inc., Cary, NC, USA). All outcome variables were checked for normal distribution and were log-transformed to achieve

an approximate normal distribution when necessary. Baseline differences between the groups were assessed using unpaired *t*-tests. To investigate whether ADT-treated prostate cancer patients are able to achieve the same beneficial effects of endurance training as an eugonadal control group of healthy men, a two-way ANOVA (group×time) with repeated measures was performed. A significant interaction indicates that the outcome variable is influenced differently by the training regimen in the two groups. Thus, only if a significant interaction was observed, a paired *t*-test for independent groups was performed to identify within-group differences from pre to

post training. A significant effect of time reflects a significant effect of the training regimen in the two groups pooled together. Results are presented as means±s.d., if not otherwise stated. *P*<0.05 was considered to be significant.

Results

Baseline characteristics

The baseline characteristics of the patient and control groups are given in Table 1. The patients had castration levels of testosterone (0.5 ± 0.4 nmol/l) that were

Table 1 Baseline comparisons between the patients and controls

	Patients (n=9)	Controls (n=10)	P value
Age (years)	67.8±6.4	68.5±3.5	0.76
Testosterone (nmol/l)	0.5±0.4	13.1±2.4	<0.001
Type 2 diabetes (n)	2 (9)	0 (10)	NA
Impaired glucose tolerance (n)	1 (9)	1 (10)	NA
Cancer characteristics			
Stage (n)			
T1a/b	1	NA	NA
T2a/b	4	NA	NA
T3a/b	4	NA	NA
Gleason score (n)			
7	1	NA	NA
8	5	NA	NA
9	3	NA	NA
ADT duration (month) ^a	9 (4–71)	NA	NA
Short-term/long-term ADT (n)	1/8	NA	NA
PSA (μg/l) ^a	0.90 (0.10–6.70)	NA	NA
Fitness			
VO _{2max} (ml(O ₂)/min per kg)	25.2±4.2	27.1±3.3	0.29
VO _{2max} (ml(O ₂)/min)	2001±424	2130±327	0.22
Blood lipids			
Total cholesterol (mmol/l)	4.7±0.8	4.7±0.9	0.81
LDL-cholesterol (mmol/l)	2.7±0.7	2.9±0.7	0.34
HDL-cholesterol (mmol/l)	1.5±0.2	1.3±0.4	0.46
Triglycerides (mmol/l)	1.53±0.68	0.96±0.34	<0.05
Glucose tolerance			
Fasting glucose (mmol/l)	6.13±1.33	5.49±0.42	0.57
Fasting insulin (pmol/l)	93.4±75.7	58.6±40.0	0.17
Glucose AUC (mmol/l)×(min)	944±385	962±184	0.22
Insulin AUC (pmol/l)×(min)	65 933±52 808	504 444±28 513	0.53
Body composition			
Weight (kg)	80.0±12.9	79.8±13.1	1.00
BMI (kg/m ²)	25.7±3.4	25.3±3.2	0.84
Lean body mass (kg)	52.3±6.6	56.3±6.6	0.33
Fat mass (kg)	24.4±7.5	20.5±7.7	0.46
Fat percentage (%)	31.1±5.6	25.7±7.0	0.17
Trunk fat mass (kg)	14.5±4.5	12.4±5.4	0.39
Inflammatory parameters			
TNFα (pg/l)	2.58±1.49	1.61±0.54	<0.05
IL6 (pg/l)	4.94±3.60	2.71±1.20	<0.05
PAI-1 (ng/l)	3.17±1.17	3.12±1.88	0.81
Leptin (pg/l)	6584±6028	3330±1922	0.19
Adiponectin (ng/l)	15 623±5842	12 793±3736	0.29

^aData are presented as means±s.d. or median (range).

significantly lower than the testosterone levels of the controls (13.1 ± 2.4 nmol/l), who were all considered eugonadal. The median PSA concentration in the patient group was $0.90 \mu\text{g/l}$ (range: 0.10 – $6.7 \mu\text{g/l}$) and the median duration of ADT was 9 months (range: 4–71 months). Eight patients were treated with long-term ADT (ADT ≥ 6 months) and one patient was treated with short-term ADT (ADT < 6 months).

At baseline, no differences existed between the two groups in age, $\text{VO}_{2\text{max}}$, and BMI. The patients had an average of 4 kg LBM less and 4 kg of FM more than those of the controls; however, none of the body composition measurements were significantly different at baseline. Plasma concentrations of $\text{TNF}\alpha$, IL6, and triglycerides were significantly higher in the patient group, whereas plasma concentrations of PAI-1, leptin, adiponectin, and cholesterol were comparable between the two groups. The measures of glucose tolerance were not different between the groups.

Training

The median compliance to the training regimen was 100% (range: 91.7–100%). During the first 6 weeks, the mean training intensity was $71.1 \pm 6.8\%$ of $\text{VO}_{2\text{max}}$, and during the last 6 weeks, it was $74.9 \pm 6.4\%$ of $\text{VO}_{2\text{max}}$. Accordingly, the subjects trained at a higher mean intensity than anticipated.

Fitness

The 12 weeks of endurance training improved $\text{VO}_{2\text{max}}$ ($\text{ml}(\text{O}_2)/\text{min}$ per kg) markedly by 11.3 ± 11.1 and $12.7 \pm 8.4\%$ in the patients and controls respectively ($P < 0.0001$). When body weight was not taken into consideration, $\text{VO}_{2\text{max}}$ ($\text{ml}(\text{O}_2)/\text{min}$) still increased significantly with $9.8 \pm 11.3\%$ in the patient group and with $12.0 \pm 9.3\%$ in the control group ($P < 0.001$). No significant group $\times$ time interactions were observed for $\text{VO}_{2\text{max}}$ ($\text{ml}(\text{O}_2)/\text{min}$ per kg, $P = 0.91$; $\text{ml}(\text{O}_2)/\text{min}$, $P = 0.99$) (Table 2), and the effect of

Table 2 Effect of endurance training on fitness, metabolic parameters, body composition, and inflammatory parameters in the blood in the patients and controls

	Patients (n=9)		Controls (n=10)		Interaction group $\times$ time	Effect of time
	Pre	Post	Pre	Post	P value	P value
Testosterone (nmol/l)	0.49 ± 0.37	0.37 ± 0.26	13.13 ± 2.4	13.72 ± 2.97	0.24	0.40
Fitness						
$\text{VO}_{2\text{max}}$ ($\text{ml}(\text{O}_2)/\text{min}$ per kg)	25.2 ± 4.2	29.0 ± 3.8	27.1 ± 3.3	31.0 ± 3.3	0.91	< 0.0001
$\text{VO}_{2\text{max}}$ ($\text{ml}(\text{O}_2)/\text{min}$)	2001 ± 424	2295 ± 585	2130 ± 327	2423 ± 308	0.99	< 0.001
Blood lipids						
Total cholesterol (mmol/l)	4.7 ± 0.8	4.7 ± 0.7	4.7 ± 1.0	4.7 ± 0.9	0.87	0.61
LDL-cholesterol (mmol/l)	2.7 ± 0.7	2.6 ± 0.5	2.9 ± 0.7	2.9 ± 0.7	0.89	0.34
HDL-cholesterol (mmol/l)	1.5 ± 0.2	1.5 ± 0.3	1.3 ± 0.4	1.4 ± 0.4	0.66	< 0.05
Triglycerides (mmol/l)	1.53 ± 0.68	1.14 ± 0.27	0.96 ± 0.34	0.97 ± 0.40	0.09	0.12
Glucose tolerance						
Fasting glucose (mmol/l)	6.13 ± 1.33	5.77 ± 0.66	5.49 ± 0.42	5.22 ± 0.38	0.72	< 0.05
Fasting insulin (pmol/l)	93.4 ± 75.7	78.3 ± 72.6	58.6 ± 40.0	56.0 ± 43.3	0.59	0.30
Glucose AUC (mmol/l) $\times$ (min)	944 ± 385	931 ± 313	962 ± 184	903 ± 158	0.24	0.21
Insulin AUC (pmol/l) $\times$ (min)	$65\,933 \pm 52\,808$	$66\,757 \pm 63\,233$	$50\,444 \pm 28\,513$	$46\,099 \pm 24\,134$	0.83	0.49
Body composition						
Weight (kg)	80.0 ± 12.9	78.5 ± 13.2	79.8 ± 13.1	78.8 ± 12.1	0.32	< 0.0001
BMI (kg/cm^2)	25.7 ± 3.4	25.2 ± 3.5	25.3 ± 3.2	25.0 ± 2.9	0.35	< 0.0001
Lean body mass (kg)	52.3 ± 6.6	52.3 ± 6.3	56.3 ± 6.6	56.2 ± 6.4	0.87	0.99
Fat mass (kg)	24.4 ± 7.5	23.1 ± 7.7	20.5 ± 7.7	19.6 ± 7.2	0.57	< 0.01
Fat percentage (%)	31.1 ± 5.6	29.8 ± 6.4	25.7 ± 7.0	25.0 ± 6.8	0.46	< 0.05
Trunk fat mass (kg)	14.5 ± 4.7	13.4 ± 4.5	12.4 ± 5.4	11.8 ± 5.0	0.37	< 0.01
Inflammatory parameters						
$\text{TNF}\alpha$ (pg/ml)	2.58 ± 1.49	2.38 ± 1.45	1.61 ± 0.54	1.78 ± 0.57	0.06	0.83
IL6 (pg/ml)	4.94 ± 3.60	3.39 ± 1.60	2.71 ± 1.20	3.78 ± 2.90	0.06	0.68
PAI-1 (ng/ml)	3.17 ± 1.17	2.40 ± 1.69	3.12 ± 1.88	2.90 ± 1.62	0.46	0.18
Leptin (pg/ml)	6584 ± 6028	4645 ± 3616	3330 ± 1922	3440 ± 2346	0.43	0.08
Adiponectin (ng/ml)	$15\,623 \pm 5842$	$15\,807 \pm 4287$	$12\,793 \pm 3736$	$12\,898 \pm 3640$	0.71	0.46

Data are presented as means $\pm$ s.d. P values for the effect of time reflect an effect of training in the two groups pooled together.

the training regimen on $\text{VO}_{2\text{max}}$ was, therefore, not different between the two groups.

Metabolic parameters

A significant effect of time for increased HDL-cholesterol concentrations ($P < 0.05$) and for decreased fasting glucose concentrations ($P < 0.05$) was achieved in response to the training regimen. No significant group $\times$ time interactions were observed for the metabolic parameters (Table 2).

Insulin sensitivity

Plasma glucose concentration was maintained at ~ 5.5 mmol/l during the clamp pre (5.41 ± 0.16 mmol/l in the patients and 5.37 ± 0.16 mmol/l in the controls) and post (5.35 ± 0.24 mmol/l in the patients and 5.38 ± 0.13 mmol/l in the controls) training. Basal and insulin-stimulated glucose R_d and R_a were similar between the two groups before the start of the training regimen. The training regimen led to no changes in basal glucose R_d ($P = 0.17$) and R_a ($P = 0.17$). Insulin-stimulated R_a was also unaffected by the training regimen ($P = 0.32$), even though eight of nine subjects in the patient group and seven of nine subjects in the control group exhibited a decreased insulin-stimulated R_a in response to the training. A significant effect of training was observed in insulin-stimulated R_d ($P < 0.05$), which increased by $14.3 \pm 19.8\%$ in the patient group and by $11.4 \pm 20.8\%$ in the control group. No significant group $\times$ time interactions were observed for either basal or insulin-stimulated R_a ($P = 0.76$ and $P = 0.40$ respectively) and R_d ($P = 0.76$ and $P = 0.77$ respectively) (Fig. 1A and B).

Western blotting

The endurance training performed in the present study increased muscle protein content of both GLUT4 and AKT ($P < 0.05$ and $P < 0.01$ respectively); however, no significant group $\times$ time effects were observed ($P = 0.62$ and $P = 0.13$ respectively) (Fig. 2A and B).

Body composition

LBM remained unchanged in response to the training ($P = 0.99$), whereas a marked reduction was observed for weight ($P < 0.0001$), BMI ($P < 0.0001$), FM ($P < 0.01$), and trunk FM ($P < 0.01$). No significant group $\times$ time interactions were observed for weight ($P = 0.32$), BMI ($P = 0.35$), LBM ($P = 0.87$), FM ($P = 0.57$), and trunk FM

Figure 1

Mean glucose R_d (A) and R_a (B) expressed as $\mu\text{mol/min per kg}$ during the basal state and during the last 30 min of the clamp pre and post 12 weeks of endurance training. Due to technical problems during the post-intervention clamp in one control subject, data are presented for $n = 9$ in the control group. Data are expressed as means $\pm$ s.d. * $P < 0.05$ for an effect of training in the two groups pooled together.

($P = 0.37$) (Table 2). The effect of the training regimen in the two groups on these parameters was thus equal.

The reduction in the amount of abdominal fat was ($P < 0.01$) 6.3 ± 4.7 and $3.9 \pm 8.3\%$ in the patient and control groups respectively in response to the training. The reduction in the amount of abdominal fat was reflected by a decrease of 8.4 ± 7.8 and $5.8 \pm 12.0\%$ in that of VAT ($P < 0.01$) and of 4.9 ± 3.5 and $2.5 \pm 8.1\%$ in that of SAT ($P < 0.05$) in the patients and controls respectively (Fig. 3A, B, and C). These changes in body composition in response to the training were, however, not different between the two groups, since no significant interactions for group $\times$ time were observed for abdominal FM ($P = 0.45$), VAT ($P = 0.56$), or SAT ($P = 0.41$). In contrast, a significant group $\times$ time interaction was observed for IMAT ($P = 0.01$). *Post hoc* analysis revealed a significant reduction of $8.5 \pm 6.8\%$ in IMAT amount in the control group ($P < 0.05$), which was not observed in the patient group ($P = 0.64$) (Fig. 3D).

Figure 2

Muscle protein content of GLUT4 (A) and total AKT (B) normalized to the intensity of the Reactive Brown (RB) total protein stain pre and post 12 weeks of endurance training. One patient refused to have biopsies taken and one sample from a control was degraded; therefore, $n=8$ in the patient group and $n=9$ in the control group. Results are reported in arbitrary units (AU). Representative blots for GLUT4 and total AKT protein expression are shown. Data are expressed as means $\pm$ s.d. * $P < 0.05$ and ** $P < 0.01$ for an effect of training in the two groups pooled together.

Inflammatory markers

The inflammatory profile did not change in response to the training, and no group $\times$ time interactions were observed for any of the measured systemic inflammatory markers, even though a tendency for an effect existed for TNF α and IL6 (both $P=0.06$) (Table 2).

Discussion

The present study was performed to elucidate whether endurance training improves insulin sensitivity and body composition in ADT-treated prostate cancer patients. Twelve weeks of endurance training improved VO_{2max} , peripheral tissue insulin sensitivity, and body composition, including a reduction in the amount of VAT. These changes were of the same magnitude as those observed in healthy control subjects. The control group achieved a reduction in the amount of thigh IMAT, which was not observed in the patient group. The present study demonstrates that endurance training can be used as an approach

to improve the overall health in prostate cancer patients receiving ADT and that normal testosterone production is not a requirement to achieve the beneficial effects of endurance training.

Recently, physical training has gained huge interest as a means to counteract the adverse side effects of the ADT given to prostate cancer patients (Segal *et al.* 2003, Galvao *et al.* 2006, 2008, 2010, 2011, Hansen *et al.* 2009, Alberga *et al.* 2012). The present study is the second to employ endurance training as a mode of exercise (Alberga *et al.* 2012), but the first to show that men with castration levels of testosterone are capable of enhancing their aerobic capacity at a magnitude comparable to that of age-matched eugonadal men. The present study, thereby, demonstrates that the castration levels of testosterone in men do not preclude an increase in aerobic capacity in response to endurance training.

Even though insulin resistance is a well-known and serious side effect of ADT in prostate cancer patients (Basaria *et al.* 2006, Smith *et al.* 2006, 2008a, Hamilton *et al.* 2011), no other studies have investigated the effect of a training intervention on insulin sensitivity in this group of patients. No significant effect of training was observed on insulin-stimulated glucose R_a . However, eight of nine subjects in the patient group actually exhibited a decreased glucose R_a during insulin stimulation, indicating that hepatic adaptations in insulin sensitivity might occur in response to endurance training. In line with previous studies carried out in non-cancer patients (Shojaee-Moradie *et al.* 2007, Lindegaard *et al.* 2008), insulin sensitivity in the peripheral tissue increased in response to the training regimen. The present study thereby highlights that testosterone ablation in men does not obstruct the ability of the peripheral tissue to increase sensitivity to insulin in response to training stimuli. The molecular mechanisms underlying this adaptation of the peripheral tissue seem to involve changes in the insulin signaling cascade. As such, muscle expression of both GLUT4 and total AKT was upregulated in response to the training regimen.

Both the patients and controls lost body weight in response to the training. In both the groups, the decline in body weight was exclusively reflected by a reduced amount of adipose tissue and was not prompted by a reduction in the amount of LBM. LBM is a crucial contributor to muscle strength, functional performance, and ultimately avoidance of accidental falls, all of which are negatively affected by ADT (Bylow *et al.* 2008, Galvao *et al.* 2009). Prostate cancer patients exhibit a continuous decrease in the amount of LBM at least 2 years after ADT

Figure 3

Abdominal fat mass (A), subcutaneous adipose tissue (B), visceral adipose tissue (C), and intermuscular adipose tissue (D) expressed as cm³ pre and post 12 weeks of endurance training. Due to metal implants in the foot, one subject in the patient group did not have MR scans performed;

therefore, $n=8$ in the patient group. Data are expressed as means $\pm$ s.d.

* $P<0.05$ and ** $P<0.01$, for an effect of training in the two groups pooled together. * $P<0.05$ for an effect of training in the control group and # $P<0.05$ between the Δ values of the two groups.

initiation (van Londen *et al.* 2008). The unchanged amount of LBM in the patient group might, therefore, be of clinical importance and emphasizes that endurance training does not seem to accelerate the loss of muscle in prostate cancer patients receiving ADT.

The present study underlines that ADT-treated prostate cancer patients are capable of reducing the amount of body fat in response to endurance training. However, one patient, who was receiving short-term ADT (<6 months), did not respond to the training regimen with regard to body composition and gained 2.6 kg of FM and lost as much as 5.0 kg of LBM (data not shown). The adverse changes in body composition primarily take place during the initial year of treatment (Greenspan *et al.* 2005, Lee *et al.* 2005, van Londen *et al.* 2008, Kim *et al.* 2011), with more than 80% of the changes occurring during the first 6 months (Smith *et al.* 2008b). We, therefore, speculate that the duration of prior ADT exposure might affect the training outcome in body composition, signifying no mitigating effect of a training intervention on the pronounced alterations in body composition during the early phase of ADT. Although speculative, this suggestion is supported by a recent study carried out by Galvao *et al.* (2011), showing increased LBM and decreased FM in long-term ADT users (>6 months) and increased FM and no change in LBM in short-term ADT

users (<6 months) in response to 12 weeks of combined strength and aerobic training.

The effect of ADT on IMAT is currently unknown. However, elevated testosterone concentration is associated with less IMAT infiltration in older men (Miljkovic *et al.* 2011) and testosterone administration dose dependently decreases the amount of IMAT in young men (Woodhouse *et al.* 2004). Thus, a rationale exists for an increased deposition of IMAT in prostate cancer patients receiving ADT. The proximity and vascular connection of IMAT to the muscle tissue probably have detrimental effects on glucose metabolism (Goodpaster *et al.* 2000, 2003, Yim *et al.* 2007, Durheim *et al.* 2008, Boettcher *et al.* 2009). The reduction in fasting glucose concentration might, therefore, in part have been mediated by the decreased deposition of IMAT in response to the training in the control group. Previous studies have shown that IMAT is modified by the level of physical activity (Manini *et al.* 2007, Durheim *et al.* 2008, Goodpaster *et al.* 2008, Murphy *et al.* 2012). The absent effect of the training intervention on IMAT in the patient group is, therefore, surprising and needs further attention in future studies.

In contrast to IMAT deposition, equal reductions were noted in abdominal fat, VAT, and SAT amounts in

response to the training. In particular, the reduction in the amount of VAT is of great importance, since the accumulation of adipose tissue in this compartment is more strongly associated with insulin resistance and type 2 diabetes compared with SAT (Bray *et al.* 2008, Preis *et al.* 2010). The reasons for this are multiple. VAT is characterized by being more inflamed than SAT with an increased secretion of, for instance, IL6 and PAI-1 (Cancello & Clement 2006). VAT is also more lipolytically active and releases more free fatty acids (FFAs) into the circulation compared with SAT (Wajchenberg *et al.* 2002). As a consequence, viscerally obese people have a higher systemic concentration of FFAs (Nielsen *et al.* 2004), which increases the risk of ectopic fat deposition in the insulin-sensitive tissue of the muscle, liver, and pancreas (Nielsen *et al.* 2004, Rossi *et al.* 2011). Furthermore, the portal vein drains VAT directly into the liver, where an increased supply of FFAs decreases the inhibition of insulin-stimulated glucose production and reduces the removal of insulin (Wajchenberg *et al.* 2002, Nielsen *et al.* 2004). Thus, the reduction in the amount of VAT is an important finding of the present study, and it may have had an effect on both peripheral tissue and hepatic insulin sensitivity, as observed in eight of nine subjects.

Systemic low-grade inflammation has previously been described in prostate cancer patients in general (Michalaki *et al.* 2004) and in some, but not all, ADT-treated prostate cancer patients (Drachenberg *et al.* 1999, Wise *et al.* 2000, Maggio *et al.* 2006, Smith *et al.* 2008a,b, Saylor *et al.* 2012). In the present study, we found an increased systemic concentration of TNF α and IL6 in the patient group compared with the control group at baseline. The lack of a non-ADT prostate cancer group makes it impossible to conclude whether it is the ADT or prostate cancer in itself that is responsible for the higher concentrations of inflammatory cytokines in the patient group. Endurance training did not alter the systemic concentrations of any of the measured inflammatory markers. These results imply that changes in inflammation status were not the major driving force underlying the improved peripheral tissue insulin sensitivity in the patient group.

Because the testing protocol was rather extensive, the number of subjects included in the study was small. This small number of subjects might, however, have concealed some beneficial effects of the training regimen or baseline differences between the patient and control groups due to a low statistical power. Also, we did not include a non-training control group of prostate cancer patients receiving ADT. This is a limitation of the study, since we are unable to conclude whether endurance training is a

true countermeasure of the ADT-induced deterioration in insulin sensitivity and body composition. However, it is important to note that the beneficial effects of exercise in the patient group were equal to those found in the healthy control group. As such, our data are clinically relevant and provide evidence for a therapeutic effect of exercise on metabolism in ADT-treated prostate cancer patients.

In conclusion, the present study demonstrates that endurance training improves insulin sensitivity in the peripheral tissue, although hepatic adaptations cannot be precluded. Endurance training also improves body composition by reducing FM and the amount of VAT in prostate cancer patients receiving ADT, implying that endurance training may lessen the detrimental side effects of ADT. A reduction in treatment side effects seems pivotal to reduce the risk of type 2 diabetes and its concomitant complications in ADT-treated prostate cancer patients. The results of the present study, furthermore, suggest that testosterone is not a prerequisite to achieve an improvement in insulin sensitivity and a reduction in the amount of abdomen-located adipose tissue in response to endurance training. In contrast, testosterone levels may be of importance for an improved deposition of IMAT in response to endurance training.

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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Author contribution statement

T Hvid, C Thomsen, P Iversen, K Brasso, K J Mikines, G van Hall, B Lindegaard, and B K Pedersen were responsible for the conception and design of the research. T Hvid, K Winding, A Rinnov, T Dejgaard, T P J Solomon, and B Lindegaard performed the experiments. T Hvid, K Winding, and T P J Solomon analyzed the data. T Hvid, K Winding, T P J Solomon, and B Lindegaard interpreted the results of the experiments. T Hvid prepared the figures. T Hvid drafted the manuscript. T Hvid, K Winding, A Rinnov, T Dejgaard, P Iversen, K Brasso, K J Mikines, B Lindegaard, and B K Pedersen edited and revised the manuscript. T Hvid, K Winding, A Rinnov, T Dejgaard, C Thomsen, P Iversen, K Brasso, K J Mikines, G van Hall, B Lindegaard, and B K Pedersen approved the final version of the manuscript.

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