Resveratrol Reduces the Levels of Circulating Androgen Precursors But Has No Effect on, Testosterone, Dihydrotestosterone, PSA Levels or Prostate Volume. A 4-Month Randomized Trial in Middle-Aged Men

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BACKGROUND. Resveratrol is a naturally occurring polyphenol with purported inhibitory effects on prostate growth and cancer development. A number of studies have demonstrated that resveratrol reduces prostate growth in animal models and reduces prostate cell growth in vitro. Based on these pre-clinical findings, interest in resveratrol is increasing in relation to the management of benign prostate hyperplasia (BPH) and prostate cancer. So far, no human trials have evaluated the effects of resveratrol on circulating androgens, prostate size, or biochemical markers of prostate size.

METHODS. In a randomized placebo controlled clinical study using two doses of resveratrol (150 mg or 1,000 mg resveratrol daily) for 4 months, we evaluated the effects on prostate size, prostate specific antigen (PSA) and sex steroid hormones in 66 middle-aged men suffering from the metabolic syndrome(MetS).

RESULTS. At baseline, prostate size and PSA were positively correlated ($R = 0.34$, $P < 0.007$) as was prostate size and age ($R = 0.37$, $P < 0.003$). Prostate size did not correlate with testosterone, free testosterone, dihydrotestosterone (DHT), or any other androgen precursor at baseline. The highest dose of resveratrol lowered the serum level of androstenedione 24% ($P = 0.052$), dehydroepiandrosterone (DHEA) 41% ($P < 0.01$), and dehydroepiandrosterone--sulphate (DHEAS) 50% ($p<0.001$), compared to the control group. However, prostate size and levels of PSA, testosterone, free testosterone and DHT remained unchanged.

CONCLUSION. In this population of middle-aged men suffering from MetS, high dose resveratrol (1,000 mg daily) administration for 4 months significantly lowered serum levels of the androgen precursors androstenedione, DHEA and DHEAS, whereas prostate size and circulating levels of PSA, testosterone, free testosterone, and dihydrotestosterone were unaffected. The present study suggests that resveratrol does not affect prostate volume in healthy middle-aged men as measured by PSA levels and CT acquired prostate volumes. Consequently, we find no support for the use of resveratrol in the treatment of benign prostate hyperplasia. *Prostate 75:1255–1263, 2015.* © 2015 Wiley Periodicals, Inc.

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INTRODUCTION

Resveratrol has been reported to possess beneficial effects in a variety of conditions including cardiovascular disease, insulin resistance, and low grade inflammation. In preclinical trials the effects of resveratrol on these conditions are persuasive [1–3]. However, the effects of resveratrol treatment in controlled clinical trials are ambiguous [4,5].

Prostate cancer and benign prostate hyperplasia (BPH) constitute considerable health problems in middle-aged and elderly men [6]. The causation in development of prostate cancer remains uncertain. However, genetic as well as hormonal and environmental factors are thought to be of importance [7,8]. Up to now more than 150 studies have been published regarding the effects of resveratrol on prostate cell lines and the prostate gland in animal models. In 2013, 39 of these were summarized by Jasinski et al. and most pre-clinical studies demonstrated that resveratrol has beneficial effects on various features of prostate health [9]. However, some studies do raise concern such as reduced survival of resveratrol treated immune-deficient mice with prostate cancer xenografts [10].

Recently, resveratrol has been shown to selectively inhibit 17,20 lyase activity of the CYP17A1 enzyme in human adrenocortical carcinoma cells, thereby reducing the androgen production [11]. Others have found that resveratrol decreases androgen receptor expression at the gene and protein level [12–14], modulates androgen receptors in prostate cancer cells [15] and stunts cell growth and differentiation [16,17].

Benign prostate hyperplasia affects approximately 90% of all men over the age of 80 [18] but the exact molecular mechanisms causing the development of BPH are not fully understood. The present treatment of BHP involves α-blockers, 5α-reductase inhibitors, surgery or a combination of these [19]. It is established that androgens are essential for maintaining BHP and that 5α-reductase in the prostate catalyses conversion of testosterone to the active dihydrotestosterone (DHT). Other androgen precursors like dehydroepiandrosterone (DHEA), androstenedione, and 5α-androstenedione may also be converted to more potent androgens in the prostate [20,21]. As resveratrol treatment of rat Leydig cells reduces androgen production [22] and possesses estrogen-like effects in itself [23], resveratrol has been proposed as a candidate for treatment of BPH [24]. Moreover, in a 3 month study of postmenopausal women receiving 1,000 mg of resveratrol per day, resveratrol seemed to modulate their systemic sex hormone status. In the study resveratrol treatment lead to an increase in urinary 2-hydroxyestrone/16α-hydroxyestrone excretion ratio and a significantly increased sex hormone binding protein (SHBG) which resulted in a calculated lower level of bioavailable testosterone [25].

Resveratrol is safe and well tolerated in high doses in humans [26]. Upon oral ingestion resveratrol is rapidly absorbed from the gastrointestinal tract but because of a rapid conjugation to sulphates and glucuronides, the concentration of intact resveratrol in the circulation is very low [27] whereas the conjugate forms are present in concentrations that are up to ~20 fold higher than the parent compound [26,28]. It is still unclear whether these conjugates might possess effects similar to resveratrol but it is possible that the conjugates have direct effects on the cells as described in the study by Polycarpou et al. [29]. The resveratrol conjugates may also serve as a reservoir of recoverable resveratrol. Most cells contain enzymes capable of removing sulphate groups [30,31] and Patel et al. have shown that resveratrol monosulphate fed to mice is absorbed and yields free resveratrol in plasma and tissues over a 6 hour period [31,32]. Thus, resveratrol sequestered in resveratrol sulphate form may be hydrolysed in the intracellular compartment providing a gradual, sustained release of resveratrol to the cell.

We recently conducted a randomized, placebo-controlled, double-blind study on the effects of two doses of resveratrol (150 mg daily and 1,000 mg daily) over a 4 month period in 66 middle-aged men suffering from the metabolic syndrome (MetS) from which we published dose dependent effects of resveratrol in increasing bone mineral density and bone specific alkaline phosphatase [33]. Since high dose resveratrol and its metabolites are non-toxic and previous preclinical and clinical trials indicate a potential to reduce prostate size and change sex hormone status respectively, exploring the clinical effects of resveratrol on prostate size and sex hormone status is highly relevant. Therefore, in a proof of concept study we investigated the effect of resveratrol on prostate size, PSA and sex hormone status in the same study population as we published the effects of resveratrol on bone parameters [33]. The hypothesis was that resveratrol might reduce the levels of androgens or block the androgen effect and thereby reduce the size

of the prostate and reduce the level of circulating PSA.

Study Design and Method

The study was a randomized, placebo-controlled, double-blind, single centre study including two doses of resveratrol. Male test subjects with MetS were randomized to treatment for four months with tablets containing placebo, 75 mg trans-resveratrol or 500 mg trans-resveratrol twice daily. Seventy-six test subjects were recruited and block randomized. Of the 76 randomized test subjects 10 dropped out or were excluded. Two were found to have cancer, two had excessive weight loss, two dropped out because of side effects and four withdrew consent not citing any reason. This left 66 test subjects eligible for evaluation of changes in prostate size, PSA and sex steroid hormones. Inclusion criteria were: Male gender, age between 30 and 60 years, and MetS. MetS was defined according to The International Diabetes Federation [34] as central obesity (Waist circumference $\geq$94 cm and/or BMI $>30\,kg/m^2$) plus any two of the following: raised triglycerides ($\geq$1.7 mmol/l), reduced high-density lipoprotein (HDL) ($\leq$1.03 mmol/l), raised blood pressure (systolic $\geq$ 130 mm Hg or diastolic $\geq$ 85 mm Hg), raised fasting plasma glucose ($\geq$ 5.6 mmol/l)—or drug treatment for the individual features. The trial was performed under conditions of weight stability, unchanged diet, unchanged dietary supplements, and strict compliance with the study drug.

Ethical Aspects

The protocol was approved by the Regional Committee on Health Research Ethics (M-20110111) and the Danish Data Protection Agency, and the study was conducted in agreement with the Declaration of Helsinki II. Participants were given oral and written information about the purpose and nature of all procedures before informed consent was obtained. The protocol was registered at clinicaltrials.gov (NCT01412645) before recruitment was initiated.

Prostate Size

Quantitative computed tomography (QCT) was performed on a Philips Brilliance 40 multidetector helical CT scanner before and after the 4 months of treatment. The CT scans were performed with the patient in a supine position and images were acquired from the acetabulum directly above the femoral head to 2 cm below the lesser trochanter, with 3-mm slice thickness and spacing. The scans were performed at 120 kV and 125 mAs/slice, rotation time, 1 sec; field of view, 360 mm; and collimation, 40×0.625 [33]. The prostate size was calculated as: ([length $\times$ height $\times$ width/2]) = Volume (mm^3). One of the authors (TNK) analysed all CT data, blinded to treatment group.

Biochemistry

Blood samples were collected between 07.30 and 11.00 o'clock after an overnight fast. Serum samples were frozen at $-80°C$, until the time of analysis. Samples were analyzed in a single batch to reduce analytical variation All steroids were measured by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) at Statens Serum Institute, 5 Artillerivej, 2300 Copenhagen S, Denmark.

The lower limit of detection (LOD) were: Estradiol (LOD)= 40 pmol/l, Estrone (LOD)= 40 pmol/l, Estrone sulphate (LOD)= 400 pmol/l, Testosterone (LOD)= 0.1 nmol/l, Androstenedione (LOD)= 0.1 nmol/l, DHEA (LOD)= 0.1 nmol/l, DHEAS (LOD)= 15 nmol/l, Progesterone (LOD)= 0.1 nmol/l, Cortisol (LOD)= 1.5 nmol/l. The CVs of the steroids were <10% in the normal range and <20% at LOD. Measurement of sexual hormone binding globulin (SHBG) was also performed at Statens Serum Institute using the Abbott Architect immunoassay (CV 8%). Free testosterone was calculated according to the Vermeulen equation using the measured values for total testosterone and SHBG. Prostate specific antigen (PSA) was measured using electrochemiluminescence, two-site immunometric assay at the Department of Clinical Biochemistry, Aarhus University Hospital in Denmark. CV of PSA measurements was 5%.

Statistics

Normality was checked by QQ-plots, and test for equal variance between groups was assessed by the Levene's test for equal variances. For PSA, prostate volume, androstenedione, DHEA, DHEAS, progesterone, estradiol estrone, and estrone sulphate log transformation resulted in normal distribution. Therefore, statistics were calculated on the log transformed values for these variables. The level of significance was 0.05. Analyses and graphs were performed with IBM SPSS Statistics (version 20), and Prism (version 5.01). Unless otherwise stated results are presented as mean $\pm$ SEM or as median with interquartile (25%;75%) range. To evaluate possible dose-dependent responses to resveratrol treatment we used linear regression analysis, and dependence between two variables was evaluated by Pearson Product Moment Correlation. Backward multiple linear regression analysis was used to investigate whether age and steroid

hormones had independent impact on PSA level or prostate volume. ANOVA with Student-Newman–Keuls post hoc adjustment was used to assess differences between groups (placebo, low-dose resveratrol, and high-dose resveratrol).

RESULTS

Baseline Characteristics

The study population comprised 66 men around 50 years of age and a mean BMI of around 34 kg/m^2. The three groups were well matched with no significant differences in baseline levels of sex steroid hormones, cortisol, PSA, or prostate size (Table I).

Age and prostate volume was correlated ($R = 0.37$, $P < 0.003$) as was age and PSA ($R = 0.36$, $P < 0.003$) and prostate volume and PSA ($R = 0.34$, $P < 0.007$). However, there was no correlation between PSA/prostate volume and any androgen (testosterone, free testosterone, and dihydrotestosterone) or any other sex steroid hormones.

At baseline, backward multiple regression analysis using prostate volume as dependent variable and all measured sex steroid hormones and age as independent variables revealed that only age and progesterone remained independent predictors of prostate volume. Age was positively correlated with prostate volume whereas progesterone was negatively related to prostate volume (Table II).

If PSA was used as dependent variable in the analysis instead of prostate volume, age remained an independent predictor of PSA. In this analysis testosterone was also an independent positive predictor of PSA level. On the other hand, SHBG and 17α-hydroxyprogesterone were both independent and negatively associated with PSA level (Table III).

Effects of Resveratrol on Steroid Hormones

The concentration of the androgen precursors androstenedione was 24% lower ($P = 0.052$), DHEA concentration was 41% lower ($P < 0.01$), and DHEAS was 50% lower in the high dose resveratrol group compared to the placebo group ($P < 0.001$) (Fig. 1A, B and C). In the low-dose resveratrol group, no significant reduction in androstenedione, DHEA, and DHEAS concentration was observed when compared to the placebo group.

Regression analysis revealed that there was a significant association between dose of resveratrol and concentration of androstenedione ($R = 0.26$, $P < 0.04$), DHEA ($R = 0.32$, $P < 0.008$), and DHEAS ($R = 0.42$, $P < 0.001$).

Regarding the other sex steroid hormones (17α-hydroxyprogesterone, testosterone, free testosterone, dihydrotestosterone, estradiol, estrone sulphate and estrone), SHBG and cortisol, no significant differences between the three groups were detected (Table IV).

TABLE I. Data are Expressed as Mean ± SEM or Median (25%–75% Percentile), NS = No Significant Difference (One Way ANOVA)

	Placebo (n = 24)	Low-dose RSV (n = 21)	High-dose RSV (n = 21)	Significance
Age	47.3 ± 1.3	48.6 ± 1.5	51.5 ± 1.3	NS
BMI (kg/m^2)	34.1 ± 0.8	33.4 ± 0.9	33.8 ± 0.7	NS
PSA	0.79 (0.57–1.07)	1.02 (0.50–1.46)	0.97 (0.63–1.4)	NS
Prostate volume (mm^3)	21657 (19360–23930)	19829 (17571–25998)	23273 (18443–28886)	NS
SHBG (nmol/l)	30.52 ± 2.20	32.38 ± 1.92	30.94 ± 2.59	NS
Progesterone (nmol/l)	0.10 (0.07–0.15)	0.08 (0.07–0.12)	0.09 (0.08–0.14)	NS
17α-hydroxyprogesterone (nmol/l)	2.51 ± 0.18	2.18 ± 0.22	2.43 ± 0.23	NS
Androstenedione (nmol/l)	1.96 (1.60–2.46)	1.74 (1.39–2.16)	1.61 (1.35–2.01)	NS
DHEA (nmol/l)	15.24 (9.32–24.27)	13.62 (8.49–20.63)	8.93 (6.20–21.25)	NS
DHEAS (nmol/l)	5792 (3726–7417)	4560 (3491–6345)	4457 (2076–5166)	NS
Testosterone (nmol/l)	11.53 ± 0.73	10.77 ± 0.63	10.94 ± 0.73	NS
Free testosterone (nmol/l)	0.29 ± 0.02	0.26 ± 0.01	0.27 ± 0.01	NS
DHT (nmol/l)	0.81 ± 0.07	0.90 ± 0.09	0.76 ± 0.07	NS
Estradiol (pmol/l)	46.75 (14.75–68.25)	45.50 (18.50–75.00)	41.50 (31.00–66.50)	NS
Estrone (pmol/l)	80.00 (55.50–112.50)	72.00 (59.00–113.50)	78.00 (56.50–102.00)	NS
Estrone Sulphate (pmol/l)	2414 (1971–3655)	2910 (1774–3619)	2691 (1913–3671)	NS
Cortisol (nmol/l)	302 (260–360)	334 (229–362)	275 (229–352)	NS

TABLE II. Multiple Regression Analysis ($R = 0.44$, $P < 0.001$). To Build the Model, Prostate Size Was Entered as Dependent Variable and Age, SHBG, 17α-hydroxyprogesterone, Androstenedione, DHEA, DHEAS, Progesterone, Testosterone, Free Testosterone, Dihydrotestosterone, Estradiol, Estrone, and Estronesulphate Were Entered in the Model as Independent Variables. (Log Values Were Used for Prostate Size, Androstenedione, DHEA, DHEAS, Progesterone, Estradiol, Estrone, and Estrone Sulphate). Then, a Backward Linear Multiple Regression Was Performed, Which Tested the Variables and Removed All Non-significant Variables

	β	*t*	Significance
(Constant)		33.984	0.000
Age	0.314	2.680	0.010
Progesterone	−0.292	−2.494	0.015

Effect of Resveratrol on Prostate Volume and PSA Level

Resveratrol treatment did not have any significant effect on prostate volume or PSA levels (Table IV). In order to detect even a very small tendency toward an effect of resveratrol we performed a simple paired *t*-test on before and after data for PSA and prostate volume separately in each of the three groups. However, even within each group there was no significant difference between before and after measurements (data not shown).

TABLE III. Multiple Regression Analysis ($R = 0.549$ $P < 0.001$). To Build the Model Psa Level Was Entered as Dependent Variable and Age, SHBG, 17α-hydroxyprogesterone, Androstenedione, DHEA, DHEAS, Progesterone, Testosterone, Free Testosterone, Dihydrotestosterone, Estradiol, Estrone, and Estronesulphate Were Entered in the Model as Independent Variables. (Log Values Were Used for PSA, Androstenedione, DHEA, DHEAS, Progesterone, Estradiol, Estrone, and Estrone Sulphate). Then, a Backward Linear Multiple Regression Was Performed, Which Tested the Variables and Removed All Non-significant Variables

	β	*t*	Significance
(Constant)		−2.659	.010
Age	0.382	3.007	0.004
SHBG	−0.323	−1.904	0.062
17α-hydroxyprogesterone	−0.348	−2.391	0.020
Testosterone	0.358	1.911	0.061

DISCUSSION

We here presented the results of what to our knowledge is the first randomized, double-blind, placebo-controlled clinical trial evaluating the effects of resveratrol on prostate size, PSA, and sex steroid hormones.

We found a significant reduction in serum levels of DHEA, DHEAS and borderline significant reduction in androstenedione in the high-dose resveratrol group compared to the control group. Resveratrol reduced the concentration of androgen precursors in a dose dependant manner, where men treated with 1,000 mg resveratrol daily had the lowest concentration. Whether an even higher dose of resveratrol would have reduced the level of these androgens further is presently unknown. From previous studies it is known that 1,000–1,500 mg resveratrol daily is well tolerated [4,33]. However, resveratrol doses of 2.5 g or more is associated with increased temporary side--effects especially gastro-intestinal discomfort [28] and therefore a daily dose of 1,000 mg seems a reasonable maximum dose to test in a clinical setting.

Our findings of reduced DHEA, DHEAS and androstenedione are in accordance with a recent publication by Oskarsson et al. [11] in which resveratrol in vitro inhibited the 17,20 lyase activity of the CYP17A1 enzyme in adrenocortical carcinoma cells. In this cell based system, resveratrol treatment resulted in a dose dependent decrease in DHEA secretion. Furthermore they found an inhibition of the conjugation of estrone to estrone-sulphate via inhibition of the SULT1E1 enzyme activity which normally catalyses the estrone sulphate conjugation. Our findings in serum from resveratrol-treated men are in accordance with these preclinical results. The estrone level in our clinical trial was unchanged whereas the estrone-sulphate level was reduced suggesting a decrease in sulphate conjugation of estrone which fits nicely with an inhibition of the SULT1E1 enzyme. In the study by Oskarsson et al. the enzyme SULT2A1, which catalyses the conjugation of DHEA with sulphate, was not affected by resveratrol. We found a reduced DHEAS concentration which may be caused by the lower amount of DHEA substrate rather than inhibition of SULT2A1. Had SULT2A1 been inhibited we would expect to see an accumulation of DHEA (or increased urinary excretion of DHEA) in conjunction with lower DHEAS levels. Furthermore, we probably would not see the resveratrol dose dependent pattern in the reduction of both DHEA and DHEAS. Overall, we found the same pattern of change in the level of androgen precursors as described in the in vitro study by Oskarsson et al. which fits nicely with an in vivo inhibition of the 17,20 lyase activity of the CYP17A1

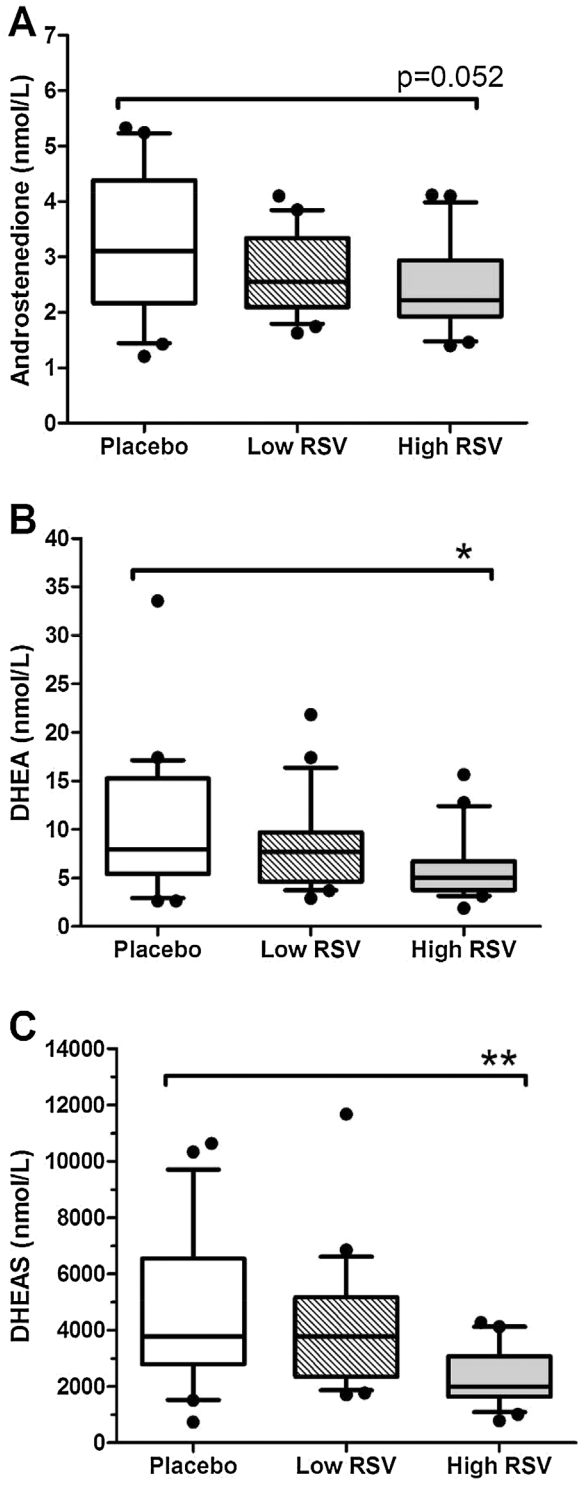

Fig. 1. Box-plot of serum concentrations of androstenedione, DHEA and DHEAS in the three groups (placebo, low-dose resveratrol (Low RSV) and high dose resveratrol (High RSV). Box Plot shows median, 10th, 25th, 75th, and 90th percentiles with outliers. (*$P < 0.01$, **$P < 0.001$).

enzyme since plasma cortisol was unaffected by resveratrol treatment. Because our study is a clinical trial, we are precluded from investigating the manner in which the 17,20 lyase activity of the CYP17A1 enzyme is inhibited. Szewczuk et al. have previously shown that resveratrol irreversibly inhibits cyclooxygenase (COX) and peroxidase activity of COX 1 by uncompetitive binding to a peroxidase substrate-COX 1 complex, while COX 2 activity was not affected [35]. Whether a similar mechanism is responsible for the inhibition of 17,20 lyase activity observed effects in our clinical trial and the study by Oskarsson et al. has to be explored in an appropriate cell based system. We anticipated an inhibition of 17,20 lyase activity would also lead to a reduced testosterone production as was the case in the in vitro study [11]. Interestingly we did not find lower levels of testosterone. This might be explained by the fact that the men in our study had intact androgen production in the testes which accounts for more than 90% of the circulating androgen levels. In an animal study of tissue distribution of resveratrol and resveratrol-glucuronide/sulphate conjugates, very low levels of intact resveratrol and resveratrol-sulphate conjugates were found in the testes [36]. We speculate that if a similar tissue distribution of resveratrol is seen in the human setting, the 17,20 lyase activity in the testes is not significantly blocked by systemic resveratrol administration.

The prostate size and PSA levels were also unchanged by resveratrol treatment. Even though lower levels of androgen precursors were achieved by high-dose resveratrol treatment and less DHEA and Androstenedione was available for conversion to testosterone in the prostate, the reduced growth stimulatory effect of this was cancelled out by the normal levels of circulating testosterone, free testosterone and DHT.

Androgens play important roles in the pathogenesis of both BPH and prostate cancer growth. Therefore, chemical or surgical castration is used to reduce androgen production when treating men with prostate cancer. By far, chemical castration is the most common course of treatment of men with an early prostate cancer diagnosis. However, in men with prostate cancer in need of a rapid drop in testosterone level (e.g., due to urinary tract outlet obstruction or impending medullary compression at diagnosis) or problems adhering to medical treatment, surgical castration is still used. In contrast to medical castration with gonadotropin releasing hormone agonists, testosterone level rapidly drops after surgical castration and deprives tumours of growth stimulus. However, surgical castration does not influence adrenal production of androgens or conversion of adrenal

TABLE IV. Data are Expressed as Mean ± SEM or Median (25–75% Percentile, NS = No Significant Difference (One Way ANOVA)

	Placebo	Low-dose RSV	High-dose RSV	Significance
PSA	0.80 (0.61–1.02)	0.77 (0.57–1.32)	0.91 (0.58–1.51)	NS
Prostate volume (mm^3)	21994 (18776–24308)	20644 (16.273–24.502)	22652 (18801–26662)	NS
SHBG (nmol/l)	30.97 ± 2.70	30.27 ± 1.86	29.81 ± 2.03	NS
17α-hydroxyprogesterone (nmol/l)	2.20 ± 0.21	1.82 ± 0.20	2.23 ± 0.22	NS
Testosterone (nmol/l)	14.08 ± 1.16	13.62 ± 0.85	13.27 ± 0.93	NS
Free testosterone (nmol/l)	0.35 ± 0.02	0.35 ± 0.02	0.34 ± 0.02	NS
DHT (nmol/l)	0.84 ± 0.09	0.83 ± 0.09	0.77 ± 0.07	NS
Estradiol (pmol/l)	29.50.(12.00–72.00)	34.00 (13.00–50.00)	16.50 (2.00–37.00)	NS
Estrone (pmol/l)	70.50 (53.00–102.50)	65.00 (42.50–88.00)	82.00 (57.00–105.50)	NS
Estrone Sulphate (pmol/l)	2727 (1805–3225)	2351 (1382–3713)	3200 (1909–4030)	NS
Cortisol (nmol/l)	295 (200–352)	278 (251–326)	250 (217–305)	NS

androgens into testosterone in the prostate. Thus, inhibition of the enzymes catalysing adrenal androgen production is an alluring prospect in this setting to achieve a further drop in testosterone levels. A complete inhibition of CYP17A1 activity blocks androgen production from all sources and such inhibitors are therefore important in the treatment of prostate cancer. Unfortunately, these compounds decrease the production of glucocorticoids which subsequently causes increased production of mineralocorticoids driven by an increase in ACTH [37]. A specific inhibition of the 17,20-lyase activity of the CYP17A1 enzyme would achieve the desired inhibition of residual androgen precursor production and stunt androgen driven cancer growth. Furthermore, as the 17α-hydroxylase activity of the CYP17A1 is left intact by resveratrol, the undesired effects of increased mineralocorticoid synthesis would be avoided [37]. Thus, our results with an intact cortisol production and a decreased production of DHEA, DHEAS and androstenedione points toward a resveratrol mediated inhibition of P450c17α-hydroxylase/17-20-lyase in the adrenal gland as the underlying mechanism. This is an interesting observation but further studies are needed in order to determine whether this effect of resveratrol is clinically relevant e.g. as adjuvant therapy in the management of prostate cancer.

A limitation of this study is the relative short study length of 4 months. However, previous studies on prostate volume and PSA levels have demonstrated that effects of the anti-androgen finasteride can be observed after 3 months treatment [38] with almost maximal effects on PSA after 6 months [39]. Therefore, we anticipate that a study period of 4 months would be sufficient to detect a change in PSA level and possibly prostate volume. Also our study group is relatively small increasing the risk of a type II error. However, our finding of a correlation between age and PSA levels as well as the correlation between PSA and prostate size is reassuring for the validity of our results as this fits well with the literature [40,41].

The strengths of our study is the randomized, placebo controlled design and use of two doses of resveratrol which showed a dose dependent effect on the levels of androgen precursors. In addition, the study population comprised of middle-aged men is relevant. As we did not detect any effect of resveratrol in the whole group we repeated the analysis after dividing the group in those having a small prostate and those with a large prostate (below or above the median prostate size (21,609 mm^3). However, we did not detect any effects of resveratrol on prostate size or PSA level regardless of the initial prostate size which further supports the observation that resveratrol does not affect these parameters.

This is a proof of concept study showing that high dose resveratrol treatment is safe and without severe adverse effects [33] and reduces the concentration of androgen precursors. Resveratrol probably reduces the concentrations of androgen precursors by inhibiting their production in the adrenal glands or by increasing urinary excretion of the androgen precursors or a combination of both. Even though relevant changes in the level of the androgen precursors were observed in our study in middle-aged men with MetS it did not result in a reduction in PSA level or prostate size.

CONCLUSION

The main findings of this study are that four months of resveratrol treatment in middle-aged men with MetS resulted in a dose dependent reduction in the concentration of the androgen precursors. High

dose resveratrol significantly reduced the androgen precursors but no changes in prostate size, PSA, testosterone, free testosterone, or DHT levels were observed. Since the present study suggests that resveratrol does not affect prostate volume in healthy middle-aged men as measured by PSA levels and CT acquired prostate volumes, we find no evidence to recommend resveratrol for the treatment of benign prostate hyperplasia.

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