Published in final edited form as:

Clin Chim Acta. 2010 August 5; 411(15-16): 1122–1125. doi:10.1016/j.cca.2010.04.011.

ACE inhibitor use was associated with lower serum dehydroepiandrosterone concentrations in older men

T Kwok¹, C Ohlsson², L Vandenput², N Tang³, YF Zhang¹, B Tomlinson¹, and PC Leung⁴

¹ Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China

² Department of Internal Medicine, Sahlgrenska University Hospital, Göteborg, Sweden

³ Department of Chemical Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong

⁴ Jockey Club Centre for Osteoporosis Care and Control, The Chinese University of Hong Kong

Abstract

Context—Angiotensin converting enzyme (ACE) activity may influence the production of adrenal androgen precursors and testosterone. Use of ACE inhibitors may therefore have an influence on serum sex hormone concentrations in older men.

Design and Methods—1486 out of 2,000 community-dwelling Chinese men aged 65 years who participated in a cohort study were randomly selected to have archived fasting morning serum analyzed for androgen precursors and sex hormones. DNA was extracted from whole blood and analyzed for ACE gene I/D polymorphism.

Results—Subjects with the ACE gene D allele (higher ACE activity) had higher serum dehydroepiandrosterone (DHEA) sulphate and DHEA than those with I/I genotype ($P=0.014$ and 0.018 respectively, Mann Whitney test). These differences were not significant after Bonferroni correction. Among those with history of hypertension, but without diabetes mellitus or cardiac failure, users of ACE inhibitors had significantly lower serum DHEA (median 1.78 versus 1.49 ng/ml in non-users, $P=0.0074$, Mann Whitney test) and also tended to have lower serum androstenedione and androst-5-ene- 3β ,17 β -diol (0.68 versus 0.72 ng/ml in non-users; 552.4 versus 624.1 pg/ml respectively, both P values <0.05). Serum testosterone and estradiol were not significantly changed.

Conclusions—ACE inhibitor use was associated with lower serum DHEA in older men.

Keywords

androgen; dehydroepiandrosterone; angiotensin converting enzyme; angiotensin converting enzyme inhibitor; gene polymorphism

Corresponding Author: Prof. Timothy Kwok, Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR. Tel 852-2632-3128; Fax 852-2637-3852, tkwok@cuhk.edu.hk.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

The renin angiotensin system (RAS) may be related to androgen production. Activation of angiotensin II type I (AT1) receptors in the hypothalamus increases secretion of luteinizing hormone [1] and corticotrophin-releasing hormone [2], which in turn stimulate androgen production in the testes and androgen precursors in the adrenal glands [3] respectively. Moreover, activation of the RAS by intravenous furosemide in normal men increased secretion of adrenal androgen precursors and an in-vitro study showed that angiotensin II had a direct effect on androgen precursor production in adrenal cells [4]. As angiotensin converting enzyme (ACE) is a major determinant of local angiotensin II concentrations, ACE activity and ACE inhibitors may influence production of androgens and their precursors in men.

There have been limited studies on the effect of ACE inhibitors on androgen metabolism in men. A prospective study of lisinopril (5-20 mg per day) in hypertensive men showed a significant decrease in free testosterone over 6 months [5], but no significant change in serum testosterone was observed in another trial of ramipril 5 mg daily for four weeks [6].

It is probably inadequate to examine testosterone in isolation, as much of the metabolic effects of testosterone mediate through estrogens [7]. In addition, 50% of androgen activity in adult men originates from adrenal androgen precursors [8], in particular, dehydroepiandrosterone (DHEA) has been shown to be important to bone health in older people [9]. Therefore when one wishes to examine the potential effects of ACE activity and ACE inhibition on sex hormones in men, a comprehensive profile on major sex hormones and androgen precursors is required.

We therefore examined the associations of systemic ACE activity and ACE inhibitor use with serum concentrations of androgens, estrogens and androgen precursors in a group of community dwelling older Chinese men. Systemic ACE activity was estimated by the determination of ACE I/D genotypes. This is a non-functional polymorphism which has been shown to have significant influence on serum and tissue ACE activity. [10,11,12].

Material and Methods

Subjects

This study was part of a multi-centre prospective cohort study of risk factors of osteoporotic fractures in older men - MrOS [13]. The research centre in Hong Kong recruited community-dwelling Chinese aged ≥ 65 y using a combination of private solicitation and public advertising from community centers and public housing estates. All subjects had the baseline measurements performed at the Jockey Club Center for osteoporosis prevention and control, the School of Public Health, the Chinese University of Hong Kong over an eighteen month period in 2001 and 2002. Written informed consent was obtained from all the subjects, and the study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

Questionnaires

A standardized, structured face-to-face interview was performed to obtain information on demographics, smoking habit, regular medications and medical history which included hypertension, diabetes mellitus and cardiac failure. Physical activity level was estimated by the Physical Activity Scale of the Elderly (PASE) - a 12-item summary scale measuring the average number of hours per day spent in leisure, household and occupational physical activities over the previous 7-day period [14].

Clinical Measurements

Body weight (Wt) was measured, with subjects wearing a light gown, by a physician balance beam scale (Healthometer, Alsip, IL), while body height (Ht) was measured by a Harpenden standiometer (Holtain Ltd, Crosswell, HK). Body mass index (BMI) was calculated thereafter using the formula: $BMI = Wt/Ht^2$. Waist circumference was measured at midway between the bottom of the ribs and the top of the hip bone.

Laboratory tests

Blood was taken after an overnight fast from all subjects. EDTA whole blood and serum samples were kept frozen at -80°C . DNA was later extracted from whole blood using standard phenol/chloroform extraction. I/D genotypes of ACE were determined by polymerase chain reaction (PCR) amplification. 25 μl PCR mixtures were set up which contained $1\times$ reaction buffer (Fermentas Life Sciences, Glen Burnie, MD), 2 mmol/l MgCl_2 , 1 μM of each forward and reverse primer, 0.2 mmol/l each dNTP, 0.6 U Taq polymerase (Fermentas Life Sciences) and 50 ng DNA. The sequences of forward and reverse primer were 5'-GAGAGACTCAAGCACGCCC-3' and 5'-ACCCAAGTGCCAGTGATGTT-3' respectively. The thermal cycling profile began with initial denaturation at 96°C for 5 min, followed by 35 cycles of 96°C for 30 s, 63.8°C for 45 s, 72°C for 30 s, and a final extension at 72°C for 10 min. Amplification products yielded were of 439 bp for the D allele and 727 bp for the I allele. The products were then separated by electrophoresis in 2 % agarose gels with ethidium bromide and were visualized under UV transillumination.

1,489 subjects were randomly selected to have stored serum analyzed for precursors—dehydroepiandrosterone sulphate (DHEAS), DHEA, Androst-5-ene- 3β , 17β -diol (5-Diol), Androstenedione (4-Dione), and bioactive hormones - testosterone, dihydrotestosterone, estrone, estradiol. All hormone assays were performed by GC/MS [15,16]. Standard samples of several concentrations were included in all assay runs to ensure precision and accuracy. Moreover, blinded aliquots of a single serum pool included in all assay runs showed no longitudinal trend in any measurement. The CV's ranged from 3.0 to 7.4%. Free fractions of testosterone and estradiol were calculated as described by Sodergard [17].

ACE genotyping was performed in the Chemical Pathology Department of the Chinese University of Hong Kong. All hormone assays were performed at the Laboratory of Molecular Endocrinology and Oncology, CHUL Research Center, Québec City, Canada. SHBG assays (Orion Diagnostics, Espoo, Finland) were performed at the Clinical Pharmacology Lab, Sahlgrenska University Hospital, Göthenburg, Sweden.

Statistical Analyses

All sex hormone data was highly skewed, and the skewness could not be resolved by common methods of transformation. Non-parametric tests were therefore adopted for group comparisons. The serum sex hormones were compared among the three ACE genotype groups by Kruskal Wallis test. Users of ACE inhibitors, angiotensin II receptor blockers, androgens or androgen inhibitors or oral corticosteroid were excluded. Clinical characteristics among the groups were compared by ANOVA and Fisher exact test.

The users of ACE inhibitors were compared with non-users in serum sex hormone concentrations by Mann Whitney test. In order to minimize the confounding effect by indication, the analysis was confined to subjects with history of hypertension but without diabetes mellitus or cardiac failure, the latter 2 medical conditions being associated with depressed serum testosterone and DHEAS respectively [18,19]. Users of angiotensin II receptor blockers, androgens or androgen inhibitors and oral corticosteroid were also excluded from this analysis. Bonferroni correction was applied because of multiple comparisons.

Results

Two thousand older Chinese men were initially recruited. ACE genotyping was successfully performed in 1841 subjects (92.1%). Out of these, 184 subjects (10%), 842 subjects (45.7%) and 815 (44.3%) had DD, ID and II genotypes respectively. The allele frequencies did not deviate from Hardy-Weinberg equilibrium. 1,489 subjects were randomly selected to have sex hormone analysis. After excluding subjects who used androgen or anti-androgen medications, ACE inhibitors, angiotensin receptor blockers or oral corticosteroid, 1156 remaining subjects had data on both genotypes and sex hormone concentrations. Their clinical characteristics were compared in Table 1. There were no significant differences in any clinical characteristic among the genotypes. The sex hormone profile of the 3 genotype groups was compared in Table 2. There were differences in DHEAS and DHEA among the three genotypes ($P=0.044$ and 0.049 respectively, Kruskal Wallis test). In particular, those with D allele tended to have higher serum DHEAS and DHEA than the I/I subjects (median 0.92 vs 0.82 ng/ml; 1.84 vs 1.66 ng/ml; $P=0.014$, 0.018 respectively; Mann Whitney test) But none of these differences were considered significant after Bonferroni correction.

Among the subjects who had sex hormone data, 208 of them were ACE inhibitor users. As expected, ACE inhibitor users were more likely to have hypertension, diabetic mellitus, cardiac failure and greater BMI than non-users (data not shown). After excluding subjects with diabetes or cardiac failure, androgen or anti-androgen medications, angiotensin receptor blockers or oral corticosteroid, the sex hormone concentrations of ACE inhibitor users and non-users among those with hypertension were compared in Table 3. The clinical characteristics of ACE inhibitor users and non-users were comparable. ACE inhibitor users had significantly lower serum DHEA (median 1.78 vs 1.49 ng/ml in non-users, $P=0.0074$, Mann Whitney test) and also tended to have lower serum 5 Diol and 4-Dione (552.4 vs 624.1 pg/ml; 0.68 vs 0.72 ng/ml for 5 Diol and 4-Dione respectively, both P values <0.05).

Discussion

This study showed that the presence of ACE gene D allele was weakly associated with higher serum DHEA and DHEAS. On the other hand, ACE inhibitor use in older hypertensive men was associated with significantly lower serum DHEA and marginally lower serum 5 Diol and 4-Dione. Overall, these findings suggest that ACE activity may be involved in the adrenal production of androgen precursors.

The subjects of this study were all apparently healthy and community dwelling. The profile of their BMI and chronic diseases was similar to other local community based studies [20,21]. The findings should therefore be generally applicable to older southern Chinese men.

The associations between ACE D allele and serum DHEAS and DHEA were not convincing as the effect did not appear to increase in a graded manner, and the p values did not reach statistical significance after Bonferroni correction for multiple comparisons. But this might have been a type I error as the number of D/D subjects was limited. In addition, although ACE I/D polymorphism has been shown to influence ACE activity in serum, heart muscle and lymphocytes[10-12], its influence on ACE activity in the organs involved in sex hormone production i.e., brain, testis and adrenal glands, has not been reported.

When analyzing the potential effect of ACE inhibitor use and serum sex hormones, it was essential to minimize the potential confounding effect by indication. Unfortunately, because of the skewness of hormone data, multiple linear regression could not be used to control for the confounding factors. Consequently we had to restrict the analysis to those with hypertension but without diabetes mellitus and cardiac failure. The remaining users and non-users of ACE inhibitors appeared to be comparable in clinical characteristics which are known to have an

effect on sex hormone metabolism. But there may still be other factors e.g., subclinical cardiovascular disease and serum lipids for which we had no data but may influence DHEA synthesis [22].

The decrease in serum DHEA associated with ACE inhibitor use was modest but significant. It was also weakly associated with lower serum concentrations of two other androgen precursors downstream. These differences were not entirely consistent with those observed among the ACE I/D genotypes. However, as fore-mentioned, the influence of this gene polymorphism on ACE activity in organ sites other than the heart is not known. Despite this inconsistency and the cross sectional nature of our data, there is a case for a randomized trial to examine the effect of ACE inhibitor on DHEA and other androgen precursors in older people.

The clinical significance of reduced DHEA production is uncertain. A significant and progressive age related decline in DHEA has been observed in men and women. A randomized placebo trial of DHEA administration in older people over 2 y showed that serum dihydrotestosterone was increased in men and serum testosterone increased in women [9]. At the same time, DHEA supplemented subjects had a significant increase in bone mineral density (BMD), but not in muscle bulk, strength or mood. If ACE inhibitors do lower DHEA production in older people, one may speculate that they have an adverse effect on BMD. Consistent with this hypothesis, a prospective cohort study of older Japanese people showed use of ACE inhibitors was associated with greater bone loss [23]. This epidemiological finding could not be explained by decreased production of angiotensin II in bone, as there are experimental and animal data to suggest that angiotensin II promotes bone loss by stimulating osteoclastic activity [24].

In contrast with a non-randomized prospective trial of lisinopril showing a significant decrease in free testosterone in hypertensive men, [5] we found no association between ACE I/D genotypes or ACE inhibitor use with serum testosterone or estradiol concentrations. The biosynthesis of testosterone is tightly regulated by biofeedback mechanisms involving the hypothalamus-pituitary-testis axis. There is experimental data to suggest that angiotensin II plays multiple roles at the level of hypothalamus and the testes. Intraventricular injection of angiotensin II induced LH secretion. [1] Leydig cells in testis express the somatic isoform of ACE heterogeneously, but possess AT1 receptors. In vitro study showed that angiotensin II had an inhibitory effect on testosterone production by Leydig cells upon stimulation by human chorionic gonadotropin and luteinizing hormone. [25] On the other hand, mature Leydig cells express a homolog of ACE – ACE2, which limits the local concentrations of angiotensin II by degrading it to angiotensin (1-7). [26]

The strengths of this study were the large sample size and the comprehensive sex hormone profiles. The limitations included its cross-sectional design. All our subjects were Chinese older men and there may be geographical or ethnic differences in sex hormone concentrations in men [27]. Our findings therefore need confirmation in men and women of other ethnic groups. The number of D/D subjects was limited by the low prevalence of this genotype among ethnic Chinese [28,29]. This has limited the power of our study to detect significant differences in sex hormone concentrations of subjects with D/D genotype. Lastly there was no information on the dosages and duration of ACE inhibitor usage in our subjects.

In conclusion, ACE inhibitor use was associated with lower serum DHEA in older men. There is a need for a randomized placebo controlled trial to confirm this association in older men and women, as this may have an adverse effect on their bone health.

Acknowledgments

This study was partially funded by the Research Grants Council Earmarked Grant CUHK4101/02M, the National Institute of Health R01 grant AR049439-01A1 and Direct Grant from the Chinese University of Hong Kong.

References

1. Steele MK, Gallo RV, Ganong WF. A possible role for the brain renin-angiotensin system in the regulation of LH secretion. *Am J Physiol* 1983;245:R805–10. [PubMed: 6318575]
2. Saavedra JM, Benicky J, Zhou J. Angiotensin II: multitasking in the brain. *J Hypertens Suppl* 2006;24:S131–7. [PubMed: 16601566]
3. Dharia S, Parker CR Jr. Adrenal androgens and aging. *Semin Reprod Med* 2004;22:361–8. [PubMed: 15635503]
4. Yanase T, Maki T, Nawata H, Kato K, Ibayashi H. Effect of angiotensin II on secretion of adrenal androgens. *Endocrinol Jpn* 1984;31:741–7. [PubMed: 6241882]
5. Koshida H, Takeda R, Miyamori. Lisinopril decreases plasma free testosterone in male hypertensive patients and increases sex hormone binding globulin in female hypertensive patients. *Hypertens Res* 1998;21:279–82. [PubMed: 9877521]
6. Gronroos PE, Irjala KM, Vesalainen RK, Kantola IM, Leinonen VM, Helenius TI, Forsstrom JJ. Effects of ramipril on the hormone concentrations in serum of hypertensive patients. *Eur J Clin Chem Clin Biochem* 1997;35:411–4. [PubMed: 9228322]
7. Riggs BL, Khosla S, Melton LJ 3rd. Sex steroids and the construction and conservation of the adult skeleton. *Endocr Rev* 2002;23:279–302. [PubMed: 12050121]
8. Labrie F, Belanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J Clin Endocrinol Metab* 1997;82:2396–2402. [PubMed: 9253307]
9. Nair KS, Rizza RA, O'Brien P, Dhatriya K, Short KR, Nehra A, Vittone JL, Klee GG, Basu A, Basu R, Cobelli C, Toffolo G, Dalla Man C, Tindall DJ, Melton LJ 3rd, Smith GE, Khosla S, Jensen MD. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 2006;355:1647–59. [PubMed: 17050889]
10. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin 1-converting enzyme gene accounting for half the variance of serum enzyme levels. *J Clin Invest* 1990;86:1343–6. [PubMed: 1976655]
11. Danser AH, Schalekamp MA, Bax WA, van den Brink AM, Saxena PR, Riegger GA, Schunkert H. Angiotensin-converting enzyme in the human heart. Effect of the deletion/insertion polymorphism. *Circulation* 1995;92:1387–8. [PubMed: 7664416]
12. Costerousse O, Allegrini J, Lopez M, Alhenc-Gelas F. Angiotensin I-converting enzyme in human circulating mononuclear cells: genetic polymorphism of expression in T-lymphocytes. *Biochem J* 1993;290(Pt 1):33–40. [PubMed: 8382480]
13. Lynn H, Kwok T, Wong SYS, Woo J, Leung PC. Angiotensin converting enzyme inhibitor use is associated with higher bone mineral density in elderly Chinese. *Bone* 2006;38:584–588. [PubMed: 16257280]
14. Washburn RA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol* 1993;46:153–162. [PubMed: 8437031]
15. Labrie F, Belanger A, Belanger P, Berube R, Martel C, Cusan L, Gomez J, Candas B, Castiel I, Chaussade V, Deloche C, Leclaire J. Androgen glucuronides, instead of testosterone, as the new markers of androgenic activity in women. *J Steroid Biochem Mol Biol* 2006;99(4-5):182–8. [PubMed: 16621522]
16. Labrie F, Cusan L, Gomez JL, Martel C, Berube R, Belanger P, Belanger A, Vandenput L, Mellstrom D, Ohlsson C. Comparable amounts of sex steroids are made outside the gonads in men and women: Strong lesson for hormone therapy of prostate and breast cancer. *J Steroid Biochem Mol Biol* 2009;113(1-2):52–6. [PubMed: 19073258]

17. Sodergard R, Backstrom T, Shanbhag V, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. *J Steroid Biochem* 1982;6(6):801–10. [PubMed: 7202083]
18. Tsai EC, Matsumoto AM, Fujimoto WY, Boyko EJ. Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone-binding globulin and body fat. *Diabetes Care* 2004;27:861–8. [PubMed: 15047639]
19. Moriyama Y, Yasue H, Yoshimura M, Mizuno Y, Nishiyama K, Tsunoda R, Kawano H, Kugiyama K, Ogawa H, Saito Y, Nakao K. The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity. *J Clin Endocrinol Metab* 2000;85(5):1834–40. [PubMed: 10843161]
20. Kwok T, Woo J, Lau E. Prediction of body fat by anthropometry in older Chinese people. *Obes Res* 2001;9:97–101. [PubMed: 11316352]
21. Thomas GN, Lao XQ, Jiang CQ, McGhee SM, Zhang WS, Adab P, Lam TH, Cheng KK, Guangzhou Biobank. Cohort Study Steering Committee. Implications of increased weight and waist circumference on vascular risk in an older Chinese population: the Guangzhou Biobank Cohort Study. *Atheroscl* 2008;196(2):682–8.
22. Sulcova J, Stulc T, Hill M, Hampl R, Masek Z, Vondra K, Ceska R. Decrease in serum dehydroepiandrosterone level after fenofibrate treatment in males with hyperlipidemia. *Physiol Res* 2005;54(2):151–7. [PubMed: 15544418]
23. Masunari N, Fujiwara S, Nakata Y, Furukawa K, Kasagi F. Effect of angiotensin converting enzyme inhibitor and benzodiazepine intake on bone loss in older Japanese. *Hiroshima J Med Sci* 2008;57(1):17–25. [PubMed: 18578363]
24. Izu Y, Mizoguchi F, Kawamata A, Hayata T, Nakamoto T, Nakashima K, Inagami T, Ezura Y, Noda M. Angiotensin II type 2 receptor blockade increases bone mass. *J Biol Chem* 2009;284(8):4857–64. [PubMed: 19004830]
25. Khanum A, Dufau ML. Angiotensin II receptors and inhibitory actions in Leydig Cells. *J Biol Chem* 1988;263:5070–5074. [PubMed: 2833494]
26. Douglas GC, O'Bryan MK, Hedger MP, Lee DK, Yarski MA, Smith AI, Lew RA. The novel angiotensin-converting enzyme (ACE) homolog, ACE2, is selectively expressed by adult Leydig cells of the testis. *Endocrinol* 2004;145(10):4703–11.
27. Santner SJ, Albertson B, Zhang GY, Zhang GH, Santulli M, Wang C, Demers LM, Shackleton C, Santen RJ. Comparative rates of androgen production and metabolism in Caucasian and Chinese subjects. *J Clin Endocrinol Metab* 1998;83:2104–9. [PubMed: 9626146]
28. Wang JG, Liu L, Zagato L, Xie J, Fagard R, Jin K, Wang J, Li Y, Bianchi G, Staessen JA, Liu L. Blood pressure in relation to three candidate genes in a Chinese population. *J Hypert* 2004;22(5):937–44.
29. Chang YC, Wu WM, Chen CH, Lee SH, Hong HS, Hsu LA. Association between the insertion/deletion polymorphism of the angiotensin I-converting enzyme gene and risk for psoriasis in a Chinese population in Taiwan. *Brit J Dermatol* 2007;156(4):642–5. [PubMed: 17263818]

Table 1

Clinical characteristics of older men by ACE I/D genotypes *

	II (N=532)	ID (N=550)	DD (N=74)
Age (y)	72.3 (5.0)	72.2 (4.9)	72.5 (5.0)
Body mass index (kg/m ²)	23.4 (3.2)	23.1 (2.9)	23.2 (3.9)
Waist circumference (cm)	86.7 (9.4)	86.5 (8.5)	86.9 (10.8)
Physical activity (PASE)	96.4 (52.7)	100.4 (51.8)	100.5 (49.3)
Current smoking (N,%)	72 (13.5)	61 (11.1)	14 (18.9)
Diabetes Mellitus (N, %)	71 (13.3)	68 (12.4)	6 (8.1)
Cardiac failure (N, %)	19 (3.6)	17 (3.1)	0 (0)
Hypertension (N, %)	177 (33.3)	187 (34.0)	24 (32.4)
Statin use (N, %)	30 (5.6)	17 (3.1)	3 (4.1)

* data presented as mean (standard deviation) unless stated otherwise; users of ACE inhibitors, angiotensin receptor blocker, androgen, androgen blockers or oral corticosteroid were excluded.

Note: PASE - Physical Activity Scale of the Elderly.

Table 2

Comparison of serum sex hormone concentrations by ACE I/D genotypes*

	II (N=532)	ID (N=550)	DD (N=74)
DHEAS (ug/ml) †	0.82 (0.55, 1.19)	0.93 (0.59, 1.31)	0.89 (0.60, 1.21)
DHEA (ng/ml) †	1.66 (1.24, 2.32)	1.85 (1.24, 2.56)	1.73 (1.27, 2.40)
4-DIONE (ng/ml)	0.72 (0.58, 0.86)	0.72 (0.56, 0.88)	0.70 (0.56, 0.82)
5-DIOL (pg/ml)	621.9 (459.7, 866.2)	655.35 (447.1, 903.9)	647.5 (455.7, 765.5)
Total-T (ng/ml)	5.34 (4.26, 6.76)	5.32 (4.26, 6.61)	5.44 (4.17, 7.34)
Total-E2 (pg/ml)	23.71 (19.04, 28.78)	23.17 (18.89, 28.20)	23.70 (19.04, 29.51)
SHBG (nmol/l)	49.83 (38.26, 61.69)	49.24 (37.95, 61.32)	50.63 (39.51, 65.65)
Free-T (ng/dl)	10.84 (8.81, 12.91)	10.77 (8.71, 12.55)	10.37 (8.46, 12.61)
Free-E (pg/ml)	0.55 (0.45, 0.66)	0.54 (0.45, 0.64)	0.54 (0.46, 0.65)
DHT (pg/ml)	447.8 (340.6, 616.7)	445.7 (328.1, 595.2)	444.7 (332.2, 592.0)
Estrone (pg/ml)	32.97 (25.89, 41.07)	33.13 (26.76, 41.16)	34.30 (27.53, 43.98)

Abbreviations: DHEA – dehydroepiandrosterone; T – testosterone; E2 –estradiol; DHT- dihydrotestosterone; 5-Diol - androst-5-ene-3 β ,17 β -diol; 4-Dione - androstenedione

* values presented as median (quartile range);107 subjects had missing ACE genotypes; Users of androgen, anti-androgen, oral corticosteroid, angiotensin converting enzyme inhibitor, angiotensin receptor blocker were excluded

† significant group differences, P <0.05, Kruskal Wallis test

Table 3

Comparison of sex hormones and metabolites in ACEI users and non-users among subjects with hypertension

*

	ACEI user (N=126)	Non-user (N= 318)	P value
Age (y, sd)	73.5 (4.8)	72.7 (4.9)	NS
Body mass index (kg/m ² , sd)	23.9 (3.2)	24.3 (3.0)	NS
Waist circumference (cm, sd)	88.4 (9.0)	89.3 (8.6)	NS
Physical activity (PASE, sd)	94.2 (44.4)	93.9 (47.4)	NS
Current smoking (N,%)	9 (7.1%)	24 (7.5%)	NS
Statin use (N, %)	12 (9.5)	20 (6.3)	NS
DHEAS (ug/ml)	0.80 (0.52, 1.21)	0.91 (0.57, 1.30)	NS
DHEA (ng/ml)	1.49 (1.06, 2.30)	1.78 (1.28, 2.46)	0.0074
4-DIONE (ng/ml)	0.68 (0.54, 0.80)	0.72 (0.58, 0.86)	0.022
5-DIOL (pg/ml)	552.4 (388.6, 714.9)	624.1 (438.4, 826.1)	0.0209
Total T (ng/ml)	4.88 (3.85, 5.99)	5.03 (4.04, 6.32)	NS
Total-E2 (pg/ml)	23.13 (18.20, 29.09)	22.79 (18.58, 28.69)	NS
SHBG (nmol/l)	46.30 (36.00, 54.64)	46.14 (35.15, 57.64)	NS
Free T (ng/dl)	10.27 (8.29, 12.01)	10.33 (8.54, 12.51)	NS
Free E (pg/ml)	0.54 (0.46, 0.67)	0.55 (0.45, 0.65)	NS
DHT (pg/ml)	406.5 (284.3, 530.9)	404.7 (308.2, 546.6)	NS
Estrone (pg/ml)	32.09 (26.09, 39.71)	32.77 (26.04, 41.13)	NS

* subjects with history of diabetes mellitus or cardiac failure, or use of androgen, anti-androgen, oral corticosteroid, angiotensin receptor blocker were excluded; data presented as median (quartile range), unless stated otherwise

Abbreviations: DHEA – dehydroepiandrosterone; T – testosterone; E –estradiol; DHT-dihydrotestosterone; 5-Diol - androst-5-ene-3 β ,17 β -diol; 4-Dione - androstenedione; ACEI – angiotensin converting enzyme inhibitor