Orlova Ya. A. [1,2], Sorokin E. D. [2], Pavlova Z. Sh.[1], Plisyuk A. G. [1,2], Kamalov A. A. [1,2]

[1] Medical Research and Educational Center, Lomonosov Moscow State University, Moscow, Russia

[2] School of Fundamental Medicine, Lomonosov Moscow State University, Moscow, Russia

Linking Cardiovascular Risk With Estradiol Level in Men

Aim	To study the relationship between the cardiovascular risk and the level of estradiol in men of young and middle age. The main group included 71 patients with newly diagnosed hyperestrogenia (HE) (serum estradiol >41.2 pg/ml). Using pseudorandomization, 68 men with normal estradiol level and age- and body weight index (BWI) – matched with the main group were included into the control group. Anthropometric data, bioimpedance variables, blood pressure (BP), and concentrations of estradiol, testosterone, glucose, and total cholesterol were analyzed in both groups.
Results	Patients of the main and control groups did not differ in age, BWI, and smoking status. Testosterone concentration was 10.18 nmol/l in the HE group and 12.18 nmol/l in the control group (p=0.006). Systolic BP was 142.0 mm Hg in the HE group and 135.2 mm Hg in the control group (p=0.011); diastolic BP was 90.3 mm Hg in the HE group and 86.2 mm Hg in the control group (p=0.008). Total cholesterol was 5.87 mmol/l in the HE group and 5.33 mmol/l in the control group (p=0.023). Blood glucose did not differ between the groups. The presence of HE in men 2.11 times (p=0.038) increased the probability of arterial hypertension. The intergroup difference by the SCORE scale did not reach statistical significance (p=0.172). BWI, waist and hip circumferences, and bioimpedance body composition parameters did not differ between the groups.
Conclusion	In the studied cohort of young and middle-aged men, HE was an independent predictor for the presence of arterial hypertension. There were no significant intergroup differences in the total risk of cardiovascular diseases calculated with the SCORE scale.

Keywords	Hyperestrogenia; cardiovascular risk; arterial hypertension; men
For citations	Orlova Ya. A., Sorokin E. D., Pavlova Z. Sh., Plisyuk A. G., Kamalov A. A. Linking Cardiovascular Risk With Estradiol Level in Men. Kardiologiia. 2023;63(9):14–19. [Russian: Орлова Я.А., Сорокин Е.Д., Павлова З.Ш., Плисюк А.Г., Камалов А.А. Оценка связи риска развития сердечно-сосудистых заболеваний с уровнем эстрадиола у мужчин молодого и среднего возраста. Кардиология. 2023;63(9):14–19].

Corresponding author	Sorokin E. D. E-mail: srknegor@gmail.com

Introduction

The prevalence of cardiovascular diseases (CVDs) increases with aging in male and female patients. However, cardiovascular pathology is 3 times more common in male patients than in premenopausal female patients, although the difference progressively decreases after menopause [1]. This necessitated a number of studies assessing the effect of sex hormones on the risk of CVDs and other age-related diseases [2]. Most experimental and clinical studies reported a protective effect of estrogens against CVDs in female patients [3]. Moreover, data were published on the positive effect of estrogens on the blood serum lipid profile, vascular function, and experimental atherosclerosis in male and female patients [4]. Until recently, the protective role of this sex steroid against CVDs was absolutized since most of the data were obtained in female and male patients with normal and reduced estrogen levels. In recent years, there have been enough studies that put this hypothesis into question in relation to male patients: hyperestrogenism in elderly male patients was associated with cardiovascular morbidity [5, 6]; higher levels of estradiol increased the risk of sudden death in male patients [7]; high-dose estrogen therapy was associated in male patients with the increased incidence of severe cardiovascular complications and higher mortality [8].

The prevalence of hyperestrogenism, a condition characterized by elevated blood levels of estrogens in male patients mainly due to 17 beta-estradiol, is indirectly estimated from 32% to 65% of the male population [9]. Hyperestrogenism can have several manifestations that reduce a man's quality of life: impotence, infertility, gynecomastia, and sarcopenia. Up to 80% of estrogens are formed in males via the conversion of androgens to estrogens by aromatase in adipose tissue. Balance of this process is very precise; several factors can change it. Obesity is the most common one. Overweight or obese male patients have elevated levels of chronic inflammation in adipose tissue, which causes multiple metabolic and immune disorders. Inflammatory processes in adipose tissue contribute to the activation of adipocyte aromatase and cause excessive

ISSN 0022-9040. Kardiologiia. 2023;63(9). DOI: 10.18087/cardio.2023.9.n2450

conversion of testosterone to estradiol. This causes decreased levels of testosterone and hyperestrogenism [10]. At the same time, obesity is a powerful risk factor for type 2 diabetes mellitus and CVDs. Estimating the effect of hyperestrogenism in male patients on the risk of CVDs irrespective of body composition may have caused heterogeneity in the results of previous studies.

Despite the interest in the role of estrogens in the pathophysiology of CVDs in male patients, there are virtually no studies on the relationship of hyperestrogenism with metabolic and CVD risk factors in young and middle-aged male patients.

Objective

Study the relationship between the risk of CVDs and estradiol levels in young and middle-aged male patients.

Material and methods

The comparative retrospective case-control clinical trial was approved by the ethics committee of the Medical Scientific Educational Center of the Lomonosov Moscow State University (Minutes No. 6/21 dated September 20, 2021).

Criteria for inclusion in the study group: male patients; encounter for preventive examination; age from 18 to 59 years; newly identified hyperestrogenism (serum estradiol>41.2 pg/mL).

Criteria for inclusion in the control group: male sex; encounter for preventive examination with symptoms of overweight, decreased performance, decreased emotional background; age from 18 to 59 years; normal levels of estradiol (serum estradiol≤41.2 pg/mL).

Exclusion criteria: previously diagnosed diabetes mellitus and/or CVD; prostate cancer and hyperplasia; known chronic inflammatory diseases (rheumatoid arthritis, systemic diseases, non-alcoholic fatty hepatosis, etc.); renal dysfunction (glomerular filtration rate<45 ml/min/1.73 m^2); hepatic dysfunction (transaminase and bilirubin levels 2 times or more higher than normal thresholds); corticosteroid therapy (within 6 months before inclusion); hyperthyroidism and hypothyroidism; hyperprolactinemia; primary or secondary hypogonadism; drug therapy affecting sex hormone axis (estrogens, androgens, aromatase inhibitors, human chorionic gonadotropin, other anabolic steroids, testosterone antagonists (ketoconazole, spironolactone, cimetidine, cyproterone).

365 medical records of male patients who successively sought preventive examination under the Male Health program were retrospectively analyzed. The main group included 71 patients with newly diagnosed hyperestrogenism (serum estradiol>41.2 pg/mL) [11]. It should be noted that the reference levels of estradiol differ significantly in different countries worldwide [11–14]. Propensity score matching was used for selecting the control group. 68 male patients with normal estradiol levels, who had comparable age and body mass index (BMI) with the main group, were selected (Table 1).

Anthropometric data (height, body weight, waist circumference (WC) and hip circumference (HC)) of all subjects were available for analysis. Blood pressure (BP) and resting heart rate (HR) data registered at examination in patient records were used. Bioimpedance measurements were made in all patients.

Serum levels of estradiol and total testosterone were determined by chemiluminescent immunoassay (Roche Cobas 6000). Biochemical blood test (total cholesterol (TC), glucose) was performed on an automatic biochemical analyzer AU480 (Beckman Coulter, Germany).

The SCORE-2 official calculator was used for the data obtained [15].

The data were processed in IBM SPSS Statistics 23.0. The Kolmogorov-Smirnov test was used to evaluate the normality of data distribution. For normally distributed characteristics, the following statistical parameters were determined: arithmetic mean (M), standard deviation (SD). For non-normally distributed characteristics, the following statistical parameters were determined: median (Me), interquartile range [Q1; Q3]. Student's t-test or Mann-Whitney's U-test were used to compare patient groups depending on the type of distribution. Absolute values and percentages were used to describe categorical variables. The significance of intergroup differences in the categorical variables was assessed based on the chi-squared test. The correlations between indicators of interest were assessed using the Spearman's correlation coefficient. The odds ratios (OR) of the presence of an indicator of interest to its absence were assessed in both patient groups. Binary logistic regression models were used to construct 95% confidence intervals (CIs) and point estimation of OR. Only one predictor was included in the univariate analysis model. Multiple binary logistic regression models were used to evaluate the effects of the indicator taking into account the contribution of other influencing variables. The statistical significance of the model was estimated by maximum likelihood. The level of statistical significance was $p<0.05$.

Results

The groups with normal and elevated estrogen did not differ in age and BMI (see Table 1). Anthropometric data and laboratory test results are presented in Table 2.

The differences in the total risk of CVDs (SCORE-2) between the groups did not reach the level of statistical significance ($p=0.172$). However, TC and BP were statistically significantly higher in patients with hyperestrogenism. This group also included more patients with known arterial

Table 1. Characteristics of the subjects

Parameter	Hyperestrogenism group	Control group	p
Age, years, Me [Q1; Q3]	44.4 [38.0; 51.0]	44.9 [36.0; 55.8]	0.525
BMI, kg/m2, M±SD	32.18±5.36	31.34±5.93	0.420

BMI, body mass index.

hypertension (AH; p=0.009). The incidence and severity of obesity, WC and HC, and glucose levels did not differ between the groups with normal and elevated estradiol. Bioimpedance findings on body composition did not differ between the patient groups. There were also no differences in smoking status. However, as well as higher levels of estradiol, lower levels of total testosterone were predictably found in the hyperestrogenism group (p=0.006). In this regard, a logistic regression analysis was carried out to assess the contribution of hyperestrogenism to the risk of AH considering the levels of endogenous total testosterone (Table 3). The presence of AH was chosen as a dependent variable for the binary logistic model. Hyperestrogenism and testosterone less than the lower limit of normal (< 12.1 nmol/L) were the influencing variables [16].

The data obtained indicate that the presence of hyperestrogenism in male patients of our sample increased 2.11-fold the probability of having AH irrespective of the levels of total testosterone.

Discussion

Current research suggests that disruption of the sex hormone axis is associated with an increased likelihood of developing CVDs. At the same time, the existing CVD risk scales do not consider these data and do not include sex hormone levels. A cross-sectional analysis of data from 122 male patients in the Framingham cohort showed that mean serum estradiol levels were significantly higher (p=0.011) in patients with coronary artery disease (CAD) than in healthy individuals. This difference in estradiol levels increased when persons older than 75 years were excluded (p<0.001). At the same time, mean serum total testosterone did not differ significantly. None of the established CVD risk factors differed between patients with CAD and control subjects, except for blood glucose, which was higher in CAD (p=0.025) [17]. A later analysis of long-term follow-up data of the Framingham cohort showed that estradiol effects change with aging. Higher levels of this hormone were associated with a lower risk of CVDs in older male patients (mean age>56 years): OR 0.86; 95% CI 0.78–0.9; p=0.005. However, in younger male patients (mean age≤56 years) estradiol levels were not associated with CVD risk: OR 1.11; 95% CI 0.89–1.38; p=0.36 [18]. In a Chinese study (n=4,720 subjects) macrovascular

Table 2. Indicators of interest in male patients depending on the presence of hyperestrogenism

Parameter	Hyperestrogenism group	Control group	p
Estradiol, pg/mL (M±SD)	49.20±6.14	26.61±26.91	< 0.001
Total testosterone, nmol/L (M±SD)	10.18±3.26	12.18±5.04	0.006
Waist circumference, cm (Me [Q1; Q3])	103.1 (94.0; 111.0)	101.5 (94.6; 109.0)	0.877
Hip circumference, cm (M±SD)	107.42±7.87	104.77±9.08	0.058
WC/HC (M±SD)	0.96±0.075	0.97±0.091	0.539
Obesity, n (%)	1 (1.5)	6 (8.8)	0.389
• Grade I, n (%)	14 (19.7)	11 (16)	–
• Grade II, n (%)	6 (8.5)	5 (7)	–
• Normal, n (%)	28 (34.4)	26 (38.2)	–
• Overweight, n (%)	22 (31)	20 (29.4)	–
AM, kg (M±SD)	31.15±11.83	29.31±11.5	0.403
AM percentage, % (Me [Q1; Q3])	29.25 [24; 33.7]	28.26 [23.9; 32.9]	0.380
LM, kg (Me [Q1; Q3])	71.79 [66.8; 77.2]	70.85 [63.83; 75.35]	0.540
SBP, mm Hg (M±SD)	142.0±16.3	135.2±15.9	0.011
DBP, mm Hg (M±SD)	90.3±10.1	86.2±9.4	0.008
Patients with AH, n (%)	46 (64.8)	29 (42.7)	0.009
Glucose, mmol/L (M±SD)	5.45±0.72	5.63±1.30	0.978
TC, mmol/L (Me [Q1; Q3])	5.87 [4.90; 6.80]	5.33 [4.58; 6.07]	0.023
Smoking, n (%)	20 (28.1)	19 (27.9)	0.976
SCORE, score (M±SD)	3.59±5.99	1.97±2.01	0.172

WC/HC waist circumference-to-hip circumference rate; FM, fat mass; LM, lean mass; SCORE, Systematic COronary Risk Evaluation.

ISSN 0022-9040. Kardiologiia. 2023;63(9). DOI: 10.18087/cardio.2023.9.n2450

Table 3. Contribution of estradiol and testosterone to the risk of arterial hypertension in young and older male patients

Parameter	OR	95% CI	p
Estradiol (> 41.2 pg/mL /≤41.2 pg/mL)	2.11	1.042–4.274	0.038
Total testosterone (> 12.1 nmol/L /≤12.1 nmol/L)	1.14	0.409–1.877	0.733

OR, odds ratio; CI, confidence interval.

complications were associated with low total testosterone, dehydroepiandrosterone, and elevated estradiol in male patients with type 2 diabetes mellitus [19]. The relationship of estradiol, rather than testosterone, with CAD was confirmed in young male patients in an invasive control study [6, 20]. Another study in a sample of elderly male patients (> 2,000 individuals) demonstrated the association of elevated estradiol with higher risk of stroke and atherosclerosis, including carotid atherosclerosis, and more frequent cases of cardiovascular and all-cause death [5, 6]. In the prospective MrOS study in elderly male patients, endogenous levels of testosterone and estradiol were not associated with an increased risk of atherosclerosis-related diseases within 8.6 years of follow-up [21].

The contradictory findings can be explained by the differences between the studied populations by age, baseline CVD risk, and the analysis methods used [22].

Our results did not reveal a relation between the total risk of CVDs (SCORE) and the serum levels of estradiol. However, it should be noted that the baseline risk of CVD was low in our study group. At the same time, hyperestrogenism was statistically significantly associated with AH in young and middle-aged male patients.

Studies in the female population showed the protective effect of elevated estradiol on the cardiovascular system, mainly due to the central influence, modulation of the renin-angiotensin-aldosterone system, and higher bioavailability of nitric oxide [23]. At the same time, statistically significant differences in the vascular effects of estrogens in perimenopausal and late postmenopausal female patients can serve as indirect confirmation of the ambivalence of hyperestrogenism effects in male and female patients [24]. Administration of 17 beta-estradiol decreased blood pressure in female mice and did not affect males, which reflects a sex-dependence of the roles of hormones in modulating cardiovascular reactions [25].

Female sex hormones can influence the regulation of fluid volume, which is an important circumstance of integrative control of systemic BP. Estrogen and progesterone were shown to alter the osmotic regulation of vasopressin, which can lead to fluid retention [26]. This mechanism may contribute to the increase in BP in young and middle-aged male patients with hyperestrogenism. Moreover, sex-related differences in the effects of estradiol may be associated with the peculiarities of the receptor apparatus. In an experimental study published in 2021 [27], models of early-stage ovarian insufficiency (OI) characteristic of perimenopause were created in young mice using 4 vinylcyclohexenediepoxide. Administration of estrogen beta receptor (ERβ) agonists was found to suppress elevated BP in an angiotensin II-induced neurotension model in females with OI but not in male mice of the same age. It was also found that the administration of ERβ agonists in females with OI but not in male patients inhibited increased signaling via N-methyl-D-aspartate receptors (NMDAR) and the production of reactive oxygen in ERβ neurons in the paraventricular nucleus of the hypothalamus, an important regulator of BP in the central nervous system [27]. Postmortem examinations in humans showed that the increased expression of Erβ correlated with higher prevalence of coronary atherosclerosis in male patients [28].

Many papers have appeared in recent years that discuss chronic inflammation as an important independent predictor of CVDs [29]. The positive correlation between estradiol and C-reactive protein levels in middle-aged and elderly male patients may reflect the pro-inflammatory effects of hyperestrogenism [30]. It was published that estradiol can increase apoptosis in endothelial cells of human coronary arteries by increasing the expression of Fas and Fas ligand [31].

In our study, hyperestrogenism was associated with higher TC (p=0.023). A study involving 111 male patients with stable CAD aged 36–73 years also found statistically significant positive correlations of estradiol levels with TC and low-density lipoprotein cholesterol [32]. High levels of estrogen are associated in female patients with a favorable blood lipid profile in most studies [33].

Unfortunately, most experimental studies on the effects of estradiol on the cardiovascular system included only female patients or female animals. In any case, it is obvious that there are sex-related differences in the pathogenesis of hypertension AH and the efficacy of antihypertensive interventions [34]. In this regard, further research of the relationship between hyperestrogenism and AH is extremely important, since elevated estradiol in male patients can independently contribute to the development of AH at a young age. Understanding the pathophysiological mechanisms may detect new targets for antihypertensive therapy.

This study has several limitations. We did not analyze the entire sex hormone axis. The study was cross-sectional and single center. The study groups were well-balanced in age, BMI, severity of abdominal obesity and smoking status, and this significantly reduced the influence of these factors on the contribution of hyperestrogenism to the development of AH. Nevertheless, the sample was relatively small. Further research is necessary to confirm and clarify the association of estrogen levels in young and middle-aged male patients with the risk of developing AH and other CVDs.

Conclusion

Hyperestrogenism in young and middle-aged male patients increased the likelihood of arterial hypertension 2.11 times (p=0.038) irrespective of body fat mass and testosterone levels.

There were no significant differences in the total risk of cardiovascular diseases (SCORE) between the groups of male patients with normal and elevated estradiol.

Funding

This study was a part of the State Assignment of the Medical Research and Educational Center of the Lomonosov Moscow State University.

No conflict of interest is reported.

The article was received on 20/03/2023

REFERENCES

1. Lu Y, Pechlaner R, Cai J, Yuan H, Huang Z, Yang G et al. Trajectories of Age-Related Arterial Stiffness in Chinese Men and Women. Journal of the American College of Cardiology. 2020;75(8):870–80. DOI: 10.1016/j.jacc.2019.12.039
2. Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Endogenous Testosterone and Mortality in Men: A Systematic Review and Meta-Analysis. The Journal of Clinical Endocrinology & Metabolism. 2011;96(10):3007–19. DOI: 10.1210/jc.2011-1137
3. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. Biology of Sex Differences. 2017;8(1):33. DOI: 10.1186/s13293-017-0152-8
4. Sudhir K, Komesaroff PA. Cardiovascular Actions of Estrogens in Men. The Journal of Clinical Endocrinology & Metabolism. 1999;84(10):3411–5. DOI: 10.1210/jcem.84.10.5954
5. Lerchbaum E, Pilz S, Grammer T, Boehm B, März W, Obermayer-Pietsch B. High Estradiol Levels are Associated with Increased Mortality in Older Men Referred to Coronary Angiography. Experimental and Clinical Endocrinology & Diabetes. 2011;119(8):490–6. DOI: 10.1055/s-0031-1284370
6. Cigankova O.V., Nikolaev K.Yu., Fedorova E.L., Bondareva Z.G. Sex hormones metabolism in men through the prism of cardiovascular risk. Journal of Atherosclerosis and Dyslipidemias. 2014;1(14):17–24. [Russian: Цыганкова О.В., Николаев К.Ю., Федорова Е.Л., Бондарева З.Г. Обмен половых гормонов в организме мужчины через призму кардиоваскулярного риска. Атеросклероз и Дислипидемии. 2014;1(14):17-24]
7. Narayanan K, Havmoeller R, Reinier K, Jerger K, Teodorescu C, Uy-Evanado A et al. Sex hormone levels in patients with sudden cardiac arrest. Heart Rhythm. 2014;11(12):2267–72. DOI: 10.1016/j.hrthm.2014.08.031
8. The Coronary Drug Project. Initial Findings Leading to Modifications of Its Research Protocol. JAMA. 1970;214(7):1303–13. DOI: 10.1001/jama.1970.03180070069012
9. Kanakis GA, Nordkap L, Bang AK, Calogero AE, Bártfai G, Corona G et al. EAA clinical practice guidelines – gynecomastia evaluation and management. Andrology. 2019;7(6):778–93. DOI: 10.1111/andr.12636
10. Lv X, Jiang Y-T, Zhang X-Y, Li L-L, Zhang H-G, Liu R-Z. Associations of sex hormone levels with body mass index (BMI) in men: a cross-sectional study using quantile regression analysis. Asian Journal of Andrology. 2023;25(1):98–102. DOI: 10.4103/aja202212
11. Basu A, Seth S, Arora K, Verma M. Evaluating Estradiol Levels in Male Patients with Colorectal Carcinoma. Journal of clinical and diagnostic research. 2015;9(1):BC08-10. DOI: 10.7860/JCDR/2015/10508.5397
12. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS et al. Maintenance of Intratumoral Androgens in Metastatic Prostate Cancer: A Mechanism for Castration-Resistant Tumor Growth. Cancer Research. 2008;68(11):4447–54. DOI: 10.1158/0008-5472.CAN-08-0249
13. Mayo Clinic Laboratories. EEST - Overview: Estradiol, Serum. [Internet] Available at: https://www.mayocliniclabs.com/test-catalog/Overview/81816
14. Chadid S, Barber JR, Rohrmann S, Nelson WG, Yager JD, Kanarek NF et al. Age-Specific Serum Total and Free Estradiol Concentrations in Healthy Men in US Nationally Representative Samples. Journal of the Endocrine Society. 2019;3(10):1825–36. DOI: 10.1210/js.2019-00178
15. Rossello X, Dorresteijn JA, Janssen A, Lambrinou E, Scherrenberg M, Bonnefoy-Cudraz E et al. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). European Journal of Preventive Cardiology. 2019;26(14):1534–44. DOI: 10.1177/2047487319846715
16. Dedov I.I., Mokrysheva N.G., Melnichenko G.A., Rozhivanov R.V., Kamalov A.A., Mkrtumyan A.M. et al. Draft of Russian Clinical Practice Guidelines "Male hypogonadism". Obesity and metabolism. 2022;18(4):496–507. [Russian: Дедов И.И., Мокрушева Н.Г., Мельниченко Г.А., Роживанов Р.В., Камалов А.А., Мкртумян А.М. и др. Проект клинических рекомендаций «Синдром гипогонадизма у мужчин». Ожирение и метаболизм. 2022;18(4):496-507]. DOI: 10.14341/omet12817
17. Phillips GB, Castelli WP, Abbott RD, McNamara PM. Association of hyperestrogenemia and coronary heart disease in men in the Framingham cohort. The American Journal of Medicine. 1983;74(5):863–9. DOI: 10.1016/0002-9343(83)91078-1
18. Ärnlöv J, Pencina MJ, Amin S, Nam B-H, Benjamin EJ, Murabito JM et al. Endogenous Sex Hormones and Cardiovascular Disease Incidence in Men. Annals of Internal Medicine. 2006;145(3):176–84. DOI: 10.7326/0003-4819-145-3-200608010-00005
19. Wang C, Zhang W, Wang Y, Wan H, Chen Y, Xia F et al. Novel associations between sex hormones and diabetic vascular complications in men and postmenopausal women: a cross-sectional study. Cardiovascular Diabetology. 2019;18(1):97. DOI: 10.1186/s12933-019-0901-6
20. Callou De Sá EQ, Feijó De Sá FC, E Silva RDS, De Oliveira KC, Guedes AD, Feres F et al. Endogenous oestradiol but not testosterone is related to coronary artery disease in men: Sex hormones and coronary artery disease. Clinical Endocrinology. 2011;75(2):177–83. DOI: 10.1111/j.1365-2265.2011.04017.x

ISSN 0022-9040. Kardiologiia. 2023;63(9). DOI: 10.18087/cardio.2023.9.n2450

21. Collet T-H, Ewing SK, Ensrud KE, Laughlin GA, Hoffman AR, Varosy PD et al. Endogenous Testosterone Levels and the Risk of Incident Cardiovascular Events in Elderly Men: The MrOS Prospective Study. Journal of the Endocrine Society. 2020;4(5):bvaa038. DOI: 10.1210/jendso/bvaa038
22. Aribas E, Ahmadizar F, Mutlu U, Ikram MK, Bos D, Laven JSE et al. Sex steroids and markers of micro- and macrovascular damage among women and men from the general population. European Journal of Preventive Cardiology. 2022;29(9):1322–30. DOI: 10.1093/eurjpc/zwaa031
23. Chakrabarti S, Lekontseva O, Davidge ST. Estrogen is a modulator of vascular inflammation. IUBMB Life. 2008;60(6):376–82. DOI: 10.1002/iub.48
24. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J et al. Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. New England Journal of Medicine. 2016;374(13):1221–31. DOI: 10.1056/NEJMoa1505241
25. Taylor LE, Sullivan JC. Sex differences in obesity-induced hypertension and vascular dysfunction: a protective role for estrogen in adipose tissue inflammation? American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2016;311(4):R714–20. DOI: 10.1152/ajpregu.00202.2016
26. Stachenfeld NS, Keefe DL. Estrogen effects on osmotic regulation of AVP and fluid balance. American Journal of Physiology-Endocrinology and Metabolism. 2002;283(4):E711–21. DOI: 10.1152/ajpendo.00192.2002
27. Milner TA, Contoreggi NH, Yu F, Johnson MA, Wang G, Woods C et al. Estrogen Receptor β Contributes to Both Hypertension and Hypothalamic Plasticity in a Mouse Model of Peri-Menopause. The Journal of Neuroscience. 2021;41(24):5190–205. DOI: 10.1523/JNEUROSCI.0164-21.2021
28. Liu PY, Christian RC, Ruan M, Miller VM, Fitzpatrick LA. Correlating Androgen and Estrogen Steroid Receptor Expression with Coronary Calcification and Atherosclerosis in Men without Known Coronary Artery Disease. The Journal of Clinical Endocrinology & Metabolism. 2005;90(2):1041–6. DOI: 10.1210/jc.2004-1211
29. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, Aspirin, and the Risk of Cardiovascular Disease in Apparently Healthy Men. New England Journal of Medicine. 1997;336(14):973–9. DOI: 10.1056/NEJM199704033361401
30. Pour HRN, Grobbee DE, Muller M, Van Der Schouw YT. Association of endogenous sex hormone with C-reactive protein levels in middle-aged and elderly men. Clinical Endocrinology. 2007;66(3):394–8. DOI: 10.1111/j.1365-2265.2007.02745.x
31. Seli E, Guzeloglu-Kayisli O, Cakmak H, Kayisli UA, Selam B, Arici A. Estradiol Increases Apoptosis in Human Coronary Artery Endothelial Cells by Up-Regulating Fas and Fas Ligand Expression. The Journal of Clinical Endocrinology & Metabolism. 2006;91(12):4995–5001. DOI: 10.1210/jc.2006-1225
32. Wranicz JK, Cygankiewicz I, Kula P, Walczak-Jedrzejowska R, Slowikowska-Hilczer J, Kula K. Endogenous Estradiol and Testosterone may Predispose toward Atherogenic Lipid Profile, but Higher Blood Level of Testosterone is Associated with Lower Number of Stenoses in the Coronary Arteries of Men with Coronary Disease. International journal of biomedical science: IJBS. 2006;2(2):135–42. PMID: 23674975
33. Palmisano BT, Zhu L, Stafford JM. Role of Estrogens in the Regulation of Liver Lipid Metabolism. Advances in Experimental Medicine and Biology. 2017;1043:227–56. DOI: 10.1007/978-3-319-70178-3_12
34. Xue B, Johnson AK, Hay M. Sex differences in angiotensin II- and aldosterone-induced hypertension: the central protective effects of estrogen. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2013;305(5):R459–63. DOI: 10.1152/ajpregu.00222.2013