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Effects of cigarette smoking, metabolic syndrome and dehydroepiandrosterone deficiency on intima-media thickness and endothelial function in hypertensive postmenopausal women

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Jolanta Mieczkowska[1ABCDEFG], **Jerzy Mosiewicz**[1ABCDEFG], **Jarosław Sak**[2ADE], **Andrzej Grzybowski**[3,4ADE], **Piotr Terlecki**[5BF], **Wojciech Barud**[1ADF], **Wojciech Kwaśniewski**[1AF], **Piotr Tutka**[6,7DEF]

[1] Department of Internal Medicine, Medical University of Lublin, Lublin, Poland
[2] Department of Ethics and Philosophical Anthropology, Medical University of Lublin, Lublin, Poland
[3] Department of Ophthalmology, Poznan City Hospital, Poznan, Poland
[4] Medical Faculty, University of Warmia and Mazury, Olsztyn, Poland
[5] Department of Vascular Surgery and Angiology, Medical University of Lublin, Lublin, Poland
[6] Department of Experimental and Clinical Pharmacology, Medical University of Lublin, Lublin, Poland
[7] Department of Health Promotion, University of Rzeszow, Rzeszow, Poland

Summary

Background: Cigarette smoking is a major risk factor of atherosclerosis. The aim of this study was to assess the relationship between smoking and arterial hypertension as well as endothelial dysfunction in postmenopausal women without clinically manifested symptoms of atherosclerosis.

Material/Methods: The study groups consisted of 35 current smokers and 45 nonsmokers. The thickness of intima-media complex (IMT), a marker of atherosclerosis, was measured in carotid arteries. Plasma concentrations of fasting glucose, insulin, lipoproteins, inflammatory markers (tumor necrosis factor-alpha, intercellular adhesion molecule-1), matrix metalloproteinases (metalloproteinase-9, tissue inhibitor of metalloproteinase-1), insulin, and dehydroepiandrosterone sulfate (DHEA-S) were measured.

Results: Smokers compared with nonsmokers showed lower fasting glucose levels in blood (87.0±10.9 and 93.2±13.6 mg/dl, $p<0.05$), higher mean systolic (131.1±15.9 $vs.$ 123.0±10.9 mm Hg, $p<0.05$) and diastolic (81.7±11.4 $vs.$ 75.2±9.2 mm Hg, $p<0.05$) blood pressure during daytime, and higher average heart rate during the daytime (78.2±9.3/min $vs.$ 71.5±9.5/min, $p<0.01$) and at night (67.2±10.6/min $vs.$ 61.7±7.7/min, $p<0.05$), respectively. The IMT in the right carotid artery was significantly higher in smokers than in nonsmokers (0.96±0.16 mm $vs.$ 0.82±0.21, $p<0.05$) and was positively correlated with smoking intensity (R=0.36) and habit duration (R=0.35). The comparison of inflammatory markers, metalloproteinases, and DHEA-S concentrations in plasma did not reveal significant differences between the 2 groups. A significant negative correlation between DHEA-S concentration in plasma and IMT in right carotid artery was found in smokers.

Conclusions: Smoking in hypertensive postmenopausal women is associated with lower fasting blood glucose and BMI values, but higher arterial pressure and heart rate, and increases in IMT in right carotid artery.

key words: cigarette smoking • menopause • vascular endothelium • arterial hypertension • cardiovascular risk factors • intima-media thickness

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BACKGROUND

Cigarette smoking is the greatest preventable cause of health disability and premature mortality around the world [1–4]. Both active and passive smoking lead to coronary atherosclerosis and are essential cardiovascular risk factors [3,5–8].

Atherosclerosis may remain asymptomatic for many years and results in sudden cardiovascular death as the first clinical manifestation. In numerous epidemiological studies the occurrence of cardiac infarcts and mortality in smokers with cardiovascular disease was proved to be several times higher than in nonsmokers [9,10]. Early detection and treatment of subclinical atherosclerosis are of great importance in prevention of myocardial infarction and sudden cardiovascular death [11,12].

The reason for sudden deaths among smokers is not only acute coronary syndrome, during which smoking frequently contributes directly to the destabilization of the atheromatous plaque, but also thrombus or embolism [13,14]. Cigarette smoking is accompanied by hypercatecholaminemia, which favors the occurrence of arrhythmia and can also contribute to sudden cardiovascular deaths reported in smokers [4,15].

Various studies have shown that cessation of cigarette smoking significantly decreases the risk of death due to coronary artery disease and other cardiovascular factors [16–18].

The coronary endothelium plays a pivotal role in controlling coronary function. Cigarette smoking is associated with endothelial dysfunction [19]. Endothelial dysfunction is manifested by impaired endothelium-dependent relaxation mediated by nitric oxide (NO) [17]. Early endothelial changes can be assessed by noninvasive diagnostic methods, such as by measuring the thickness of intima-media complex (IMT), before clinical symptoms of atherosclerosis and coronary artery disease appear [20,21]. The IMT is believed to be a validated marker for the process of atherosclerosis and cardiovascular mortality [11,22,23]. IMT measured within carotid arteries correlates with the progression of the atherosclerotic changes in coronary, femoral, brachial and cerebral arteries [22–24]. Monitoring of IMT appears to be useful in preventing or retarding the development of atherosclerosis and hence the risk of coronary artery disease [25].

Epidemiological studies revealed that approximately 24% of women in Poland are smokers [26]. In our study, conducted in the Lublin region, 28.3% of women over 45 years of age were smokers [27]. In smoking women, especially those who are postmenopausal, cardiovascular risk factors are more intensified, and plasma lipid levels and arterial blood pressure values are higher [28]. As with atherosclerosis, endothelial dysfunction in women appears to increase with age. Impairment of endothelial function and development of atherosclerosis in postmenopausal women may result from a deficiency of sex hormones, including adrenal androgen and dehydroepiandrosterone sulfate (DHEA-S) [29,30].

The present study was designed to determine the relationships of cigarette smoking with IMT in the carotid arteries and the activity of endothelial inflammatory markers in postmenopausal hypertensive women with other cardiovascular risk factors. Additionally, the relationship between concentration of dehydroepiandrosterone sulfate (DHEA-S) in

plasma and the endothelial function in smoking postmenopausal hypertensive women was studied.

MATERIAL AND METHODS

Study participants

The study included 80 postmenopausal women with uncomplicated arterial hypertension. First, participants were screened by inclusion criteria. Women were subjected to initial testing using their smoking history. Within the screening phase women were divided into 2 groups. Thirty-five, aged 52.2±4.8, were active smokers. According to the criteria of the WHO, smokers were people who had smoked, for at least 6 months, 1 or more cigarettes per day [31]. Mean duration of smoking habit was 20.3±7.9 years. Subjects smoked an average of 16.5±6.9 cigarettes per day. The second group included 45 nonsmokers, aged 52.6±4.8. Ex-smokers were excluded from the nonsmokers group.

Postmenopausal women were defined according to the following criteria: 1) duration of amenorrhea >12 months, 2) the presence of hot flashes/sweats, and 3) the blood concentration of follicle stimulating hormone (FSH) >30 IU/ml [32]. We excluded patients who had either clinical or laboratory evidence of serious or unstable disorders like coronary artery disease, stroke or other cerebrovascular events, heart failure, cardiomyopathy, diabetes and other severe systemic or organ diseases. Women treated with hormonal replacement therapy were also excluded from the study.

Medical history data and the results of physical examination were registered in a questionnaire. Waist circumference was measured and body mass index (BMI) and waist-hip ratio (WHR) were calculated. Waist circumference was taken as the minimum circumference between the umbilicus and xiphoid process and was measured to the nearest 0.5 cm. BMI was calculated as weight in kilograms divided by the square of height in meters.

The patients usually took angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and/or beta adrenergic receptors antagonists as antihypertensive treatment. The use of antihypertensive drugs was evenly distributed within both study groups.

Drugs that block the renin-angiotensin-aldosterone system were taken by 19.9% of patients in the smoking group (ramipril – 17.2%, telmisartan – 2.8%) and 13.3% from the nonsmoking group (ramipril – 11.1%, telmisartan – 2.2%) (Wald's χ^2 0.02, OR: 0.92 [95%CI: 0.25–3.38], p=0.9). Beta-blockers (metoprolol) were taken by 8.6% of patients in the smokers' group and 15% of the nonsmokers. (Wald's χ^2 0.86, OR: 1.96 [95% CI: 0.46–8.42], p=0.36). Mean values of systolic and diastolic blood pressure at daytime and night and the percentage of raised values of systolic and diastolic blood pressure at daytime and at night observed in patients treated and untreated with antihypertensive drugs did not differ in a statistically significant way.

The experimental protocol was approved by the Medical University of Lublin Ethics Committee (KE-0254/184; 185/2006). All the examinations were performed with the written informed consent of the patients. Also, written

informed consent was obtained from all participants for data analysis and reporting.

Determination of blood pressure

During 2 visits to a physician, systolic (RRs) and diastolic (RRd) arterial blood pressure were taken after at least 10-minute rest twice at each visit. Patients were considered hypertensive when their RRs ⩾140 mm Hg and/or RRd ⩾90 mm Hg, or when they were in the course of antihypertensive treatment.

In all investigated patients, 24-hour arterial blood pressure and heart rate (HR) monitoring by the Holter method was performed. Measurements of systolic and diastolic blood pressure (DRRs and DRRd, respectively) were performed 3 times per hour during the day and twice per hour at night (NRRs and NRRd, respectively). During the day the values of RRs ⩾135 mm Hg, RRd ⩾85 mm Hg, and at night: RRs ⩾120 mm Hg, RRd ⩾70 mm Hg were assumed as elevated [33]. The obtained results were processed by the OXFORD computer program.

Biochemical measurements

Overnight fasting plasma was collected and immediately processed by the laboratory for the measurements of total cholesterol, low-density lipoprotein-cholesterol (LDL-Ch), high-density lipoprotein-cholesterol (HDL-Ch), triglycerides (TG), glucose, metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), intercellular adhesion molecule-1 (ICAM-1), tumor necrosis factor-alpha (TNF-α), insulin, and DHEA-S.

Total cholesterol, LDL-Ch, HDL-Ch and TG concentrations in plasma were measured using bio-Merieux tests and COBAS INTEGRA 600 analyzer (Roche, Tokyo, Japan). Fasting plasma glucose concentration was determined by enzymatic method with glucose oxidase using bio-Merieux tests and COBAS INTEGRA 600 analyzer (Roche, Tokyo, Japan).

The concentrations of metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), intercellular adhesion molecule-1 (ICAM-1), tumor necrosis factor-alpha (TNF-α) and insulin were determined in plasma using the immunological test (R&D Systems, Minneapolis, MN, USA) and the enzyme-linked immunosorbent assay (ELISA) method (ELx 800, Bio-Tek Instrument INC, Vermont, USA). The plate was first read at 450 nm against a reference filter set at 650 nm (or 630 nm). Insulin resistance (IR) was calculated according to homeostasis model assessment (HOMA): IR = [fasting insulin concentration (μIU/ml) × fasting glucose concentration (mmol/l)]/22.5 [34].

The concentration of DHEA-S in plasma was measured using radioimmunoassay (RIA) method by means of gamma radiation meter LBIS 501 (Berthold Technologies, Bad Wildbad, Germany).

All assays were performed by personnel unaware of the clinical data.

Metabolic syndrome

Metabolic syndrome was diagnosed on the basis of the following criteria: waist circumference ⩾80 cm and additionally 2 out of 4 cardiovascular risk factors: 1) plasma fasting glucose concentration >100 mg/dl, 2) arterial blood pressure >135/80 mm Hg (an average measurement was registered twice) or hypertension diagnosed earlier, 3) plasma HDL-Ch concentration <50 mg/dl, and 4) plasma TG concentration >150 mg/dl [35]. Plasma concentration of LDL-Ch >100 mg/dl was assumed above normal.

Intima-media thickness measurement

The condition of arterial vessels was assessed on the basis of ultrasonographic measurement of IMT in both carotid arteries. Doppler method examinations of carotid arteries were performed using Acuson X300 (Siemens, Berlin, Germany) linear probe of variable frequency 5–10 MHz. All measurements were performed by a trained sonographer. The scanning of extracranial carotid arteries in the neck was conducted bilaterally at longitudinal projections and at transverse projections for measurement of IMT 1 cm below the carotid bifurcation. Each carotid wall and segment was explored to identify the thickest intima-media sites. IMT was measured as the distance between the lumen-intima interface and the media-adventitia interface on the B-mode image.

Statistical analysis

Data were processed using the Statistica 5 (StatSoft) computer program. Data are shown as mean (with minimum and maximum values as well as 95% confidence interval [CI]) ± standard deviation (SD). Differences between groups were compared using parametric and nonparametric tests. Compatibility of distribution of the studied variables with normal was examined using the Kolmogorov-Smirnov test. Variables with distribution significantly different from normal distribution were compared using Mann-Whitney test (HR during the day, NRRs, percentage of evaluated values of NRRs, BMI, IMT of right carotid artery). To compare the other parameters of normal distribution, Student's t-test was used. Correlations between selected parameters were calculated using nonparametric test (R-Spearman's rank correlation coefficient). Measurements of RRS, RRd and HR at daytime and night as well as IMT of carotid arteries were correlated with duration and intensity of smoking habit (the number of cigarettes smoked per 24 hours). Correlations of IMT of carotid arteries with DHEA-S level in plasma were calculated.

The groups of smoking and nonsmoking women were compared in relation to the incidence of metabolic syndrome using logistic regression method, calculating Wald's χ^2, odds ratio (OR) and 95% confidence intervals (95% CI). P value of <0.05 was considered statistically significant.

RESULTS

Clinical and metabolic characteristics of study participants

There were 35 women in the group of smokers (group 1) and 45 in the group of nonsmokers (group 2). The average age of smokers (52.2±4.8) and nonsmokers (52.6±4.8) did not differ significantly. Table 1 shows anthropometric and biochemical features in both studied groups. BMIs were significantly

Table 1. Anthropometric and biochemical features of smoking and nonsmoking postmenopausal women.

	Smokers mean±SD (min.–max.) (95%CI)	Nonsmokers mean±SD (min.–max.) (95%CI)	p
Waist circumference (cm)	85.8±15.0 (60–135) (80.6–90.3)	91.5±14.1 (68–130) (86.7–96.1)	0.08
BMI (kg/m2)	26.2±5.9 (17–51) (24.0–28.3)	28.7±5.2 (20.7–40.9) (27.2–30.3)	<0.05
WHR	0.82±0.07 (0.68–0.96) (0.80–0.84)	0.84±0.06 (0.73–0.97) (0.82–0.85)	0.30
Total cholesterol (mg/dl)	216.1±36.9 (145.0–325.0) (203.2–228.9)	227.2±45.2 (147–392) (213.4–240.9)	0.25
LDL-cholesterol (mg/dl)	134.7±33.4 (83–214) (123–146.4)	142.5±45.9 (79–318) (128.6–156.5)	0.40
HDL-cholesterol (mg/dl)	62.2±16.8 (36–104) (56.4–68.1)	60.6±1.8 (34–100) (56.8–64.5)	0.63
Triglycerides (mg/dl)	112.6±58.8 (46–316) (91.7–133.5)	122.5±79.3 (42–455) (98.4–146.6)	0.55
Glucose (mg/dl)	87.0 ±10.9 (68.0–112.0) (83.8–91.3)	93.2±13.6 (72.0–123.0) (89.2–97.3)	<0.05
TIMP-1 (ng/ml)	223.0±81.4 (74.3–422.6) (179.7–266.4)	225.3±74.7 (122.8–432.2) (194.4–256.1)	0.92
MMP-9 (ng/ml)	158.9±113.7 (24.5–394.6) (98.4–219.6)	135.6±78.2 (32.3–351.3) (99.7–171.6)	0.46
TNF-α (pg/ml)	4.8±1.63 (1.6–11.4) (3.3–6.3)	5.09±2.8 (0.6–12.6) (4.7–7.2)	0.45
ICAM-1 (ng/ml)	328.9±88.4 (189.1–499.6) (279.9–377.8)	365.2±99.2 (208.4–621.5) (323.2–406.9)	0.26
Insulin (µIU/ml)	15.9±7.9 (5.2–37.9) (12.6–19.1)	17.6±13.7 (5.7–65.9) (11.6–23.5)	0.59
HOMA index	3.3±1.6 (1.3–7.7) (2.6–3.9)	3.8±2.8 (1.7–12.8) (2.54–5.01)	0.46
DHEA-S (µg/ml)	124.8±59.2 (41.0–208.0) (103.4–146.2)	138.2±70.2 (6.0–248.0) (118.8–159.5)	0.39

Data are shown as mean (with minimum and maximum values as well as 95% confidence interval – CI) ± standard deviation (SD). BMI – body mass index; WHR – waist-hip ratio; TIMP-1 – tissue inhibitor of metalloproteinase-1; MMP-9 – metalloproteinase-9; TNF-α – tumor necrosis factor-alpha; ICAM-1 – intercellular adhesion molecule-1; HOMA index = [fasting insulin concentration (µIU/ml) × fasting glycemia level (mmol/l)]/22.5; DHEA-S – dehydroepiandrosterone sulphate.

higher in nonsmokers (28.7±5.2) than in smokers (26.2±5.9) ($p<0.05$). Mean total cholesterol, LDL-Ch, HDL-Ch, and TG were comparable in both groups. Mean fasting glucose concentration was significantly higher (93.2±13.6) in nonsmokers than smokers (87.0±10.9) ($p<0.05$). The incidence of metabolic syndrome was higher among nonsmokers (46.2%) compared with smokers (22.4%) (χ^2 Wald's 2.93, OR 2.31 [95% CI: 0.87–6.12], $p=0.08$). However, the difference between both groups did not reach statistical significance.

Blood pressure

In smokers and nonsmokers mean values of RRs and RRd as well as the percentage of elevated values of DRRs, DRRd, NRRs and NRRd in 24-hour monitoring were compared.

Mean DRRs, DRRd, NRRs but not NRRd were significantly higher in smokers than in nonsmokers (Table 2). Mean HR was also statistically significantly higher in smokers in comparison with nonsmokers, being 78.2±9.3/min and 71.5±9.5/min ($p<0.01$) during the day and 67.2±10.6/min and 61.7±7.7/min ($p<0.05$) at night, respectively. In smokers a statistically significant higher percentage of elevated values of DRRs, DRRd, and NRRs was also observed compared with those of nonsmokers ($p<0.05$) (Figure 1).

The mean DRRs and DRRd significantly correlated with the duration of the habit. No significant correlations were found between the habit duration and NRRs and NRRd. Habit duration correlated significantly with HR at daytime, but not at night (Figure 2).

Table 2. Systolic and diastolic arterial blood pressure at daytime and night in smoking and nonsmoking postmenopausal women.

	Smokers	Nonsmokers	p
DRRs (mm Hg)	131.1±15.9	123.0±10.9	<0.05
DRRd (mm Hg)	81.7±11.4	75.2±9.2	<0.05
NRRs (mm Hg)	111.2±28.5	108.7±10.2	0.65
NRRd (mm Hg)	70.6±11.8	65.7±7.6	0.06

Data are shown as mean ± standard deviation (SD). DRRs – systolic blood pressure at daytime; DRRd – diastolic blood pressure at daytime; NRRs – systolic blood pressure at night; NRRd – diastolic blood pressure at night.
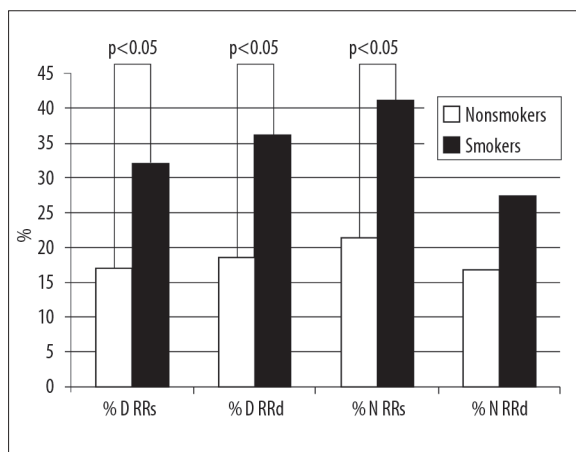

Figure 1. Comparison of elevated values of systolic and diastolic arterial blood pressure at daytime and at night in smokers and nonsmokers in postmenopausal women. Graph bars represent percentages of elevated values of arterial blood pressure. % DRRs – percentage of elevated values of systolic blood pressure at daytime, % NRRs – percentage of elevated values of systolic blood pressure at night, % DRRd – percentage of elevated values of diastolic blood pressure at daytime, % NRRd – percentage of elevated values of diastolic blood pressure at night.

The number of cigarettes smoked per 24 hours did not influence the mean values of DRRs, DRRd, NRRs and NRRd. However, the number of cigarettes smoked correlated in a statistically significant way with HR during the day (Figure 3).

Inflammatory markers and metalloproteinases

The comparison of inflammatory markers and metalloproteinases concentrations in plasma did not reveal significant differences between smokers and nonsmokers (Table 1). No statistically significant correlations were found between TIMP-1, MMP-9, ICAM-1, and TNF-α plasma concentrations and the number of cigarettes smoked per 24 hours or the duration of the habit.

Dehydroepiandrosterone sulfate

Mean plasma DHEA-S concentrations were not different between the 2 studied groups (Table 1). In smokers the negative correlation between DHEA-S concentration and IMT of right carotid artery was statistically significant ($p<0.05$) (Figure 4).

Intima-media thickness

The IMT in left and right carotid arteries were compared in smoking and nonsmoking women. The IMT in the right carotid artery was significantly higher in smokers (0.96±0.16 mm) than in nonsmokers (0.82±0.21 mm) ($p<0.05$) (Figure 5). The IMT in the right carotid artery was positively correlated with cigarette smoking intensity and habit duration (Figure 6). The IMT in the left carotid artery were 0.83±0.17 mm and 0.77±0.23 mm in smokers and nonsmokers, respectively (not significant).

DISCUSSION

Our studies revealed that in 24-hour arterial blood pressure monitoring in hypertensive postmenopausal women who smoked cigarettes, compared with nonsmokers, higher mean values of RRs and RRd were observed at daytime as well as higher percentage of raised values of RRd and higher mean HR. At night, higher mean values of RRs and mean HR were also demonstrated in smokers. This may imply both acute changes, directly dependent on smoking a cigarette, and long-term changes in the activity of the adrenergic system in smokers.

Minami et al. [36] found that cigarette smoking is associated with transitory increases in blood pressure. It is believed that the increases in blood pressure are caused by direct stimulation of sympathetic nerve endings and are related to nicotine because they are not observed with nicotine-free cigarettes [17,37].

Nicotine activity at the moment of smoking a cigarette, causing increased adrenalin secretion, leads to a short-term increase in arterial pressure and HR, as an effect of vasospastic response to stimulation of the adrenergic system [15,36,38]. Our studies demonstrate that in hypertensive smoking women the increase in arterial pressure maintains for a longer time, also at night, and appears more frequently than in nonsmokers.

The observed differences in arterial pressure between smokers and nonsmokers may result from the damage of baroreceptors in hypertensive patients, larger in smokers than in nonsmokers. Observations of Shinozaki et al. [39] revealed a different vascular response in healthy smokers and smokers with coronary artery disease. Cigarette smoking in the healthy group decreased muscle sympathetic nerve activity, whereas in the group of smokers with coronary artery disease this activity was significantly increased. Sensitivity of baroreceptors to pressure factors was decreased in the
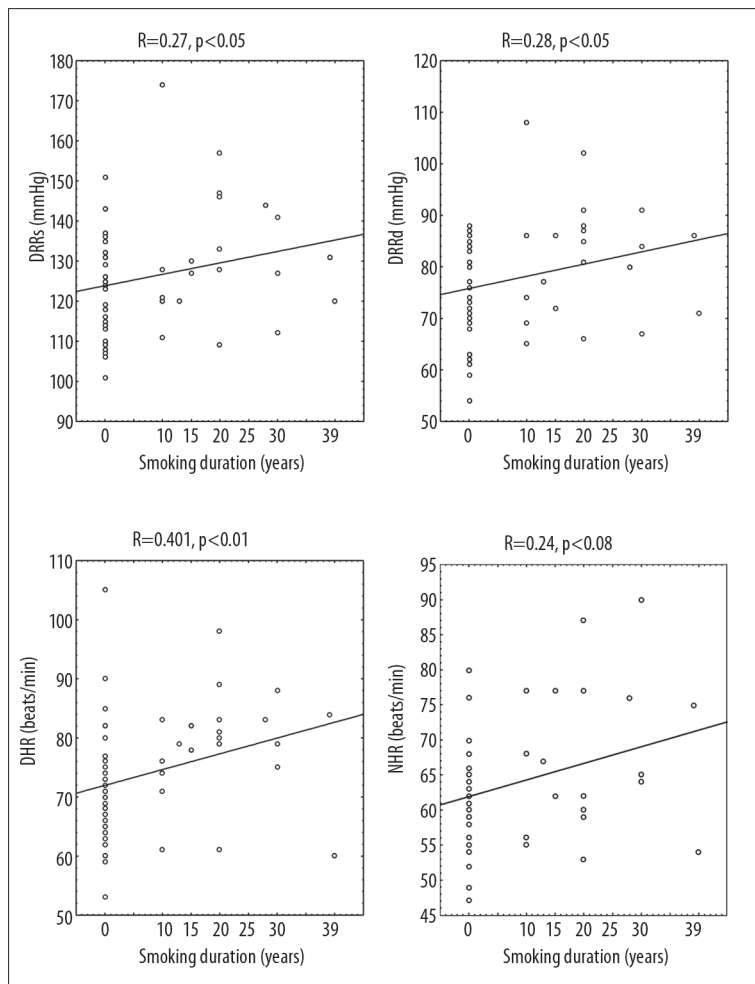
Figure 2. Correlation of systolic, diastolic blood pressure and heart rate with smoking duration in smokers and nonsmokers in postmenopausal women. R – Spearman's rank correlation coefficient, DRRs – systolic blood pressure at daytime, DRRd – diastolic blood pressure at daytime, DHR – heart rate at daytime, NHR – heart rate at night.
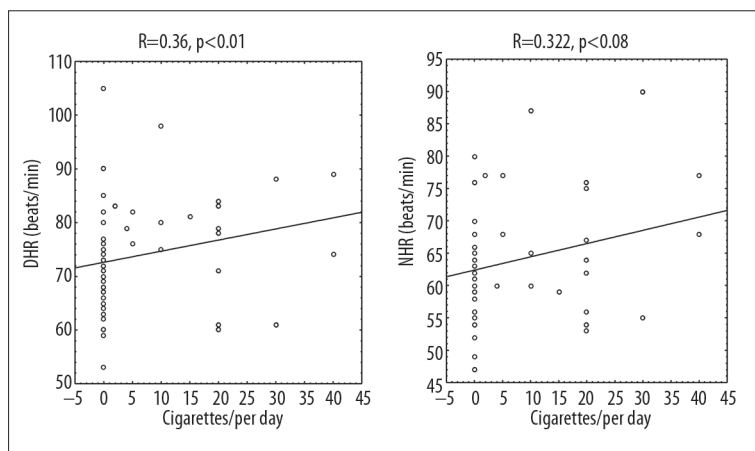

Figure 3. Correlation of heart rate at daytime (DHR) and at night (NHR) with cigarette smoking intensity in smokers and nonsmokers in postmenopausal women. R – Spearman's rank correlation coefficient.

group of men with coronary artery disease, and was negatively correlated with muscle sympathetic nerve activity. Thus, cigarette smoking increased muscle sympathetic activity in smokers with damaged reflex from baroreceptors.

The more frequent and higher increases in blood pressure observed in hypertensive smokers may also be the effect of greater imbalance between vasoconstrictive and vasodilatative factors coming from endothelium in response

to cigarette smoking. Smoking results in the damage of vascular endothelium by generating free radicals, and the loss of vasodilatation ability largely depends on the reduced endothelial production of the most essential vasodilator – NO [40]. The exact mechanism by which smoking impairs NO-mediated endothelial function has not been fully elucidated.

Lin et al. [41] found a significant dependence of the structure (size of intima-media measurement) and function of
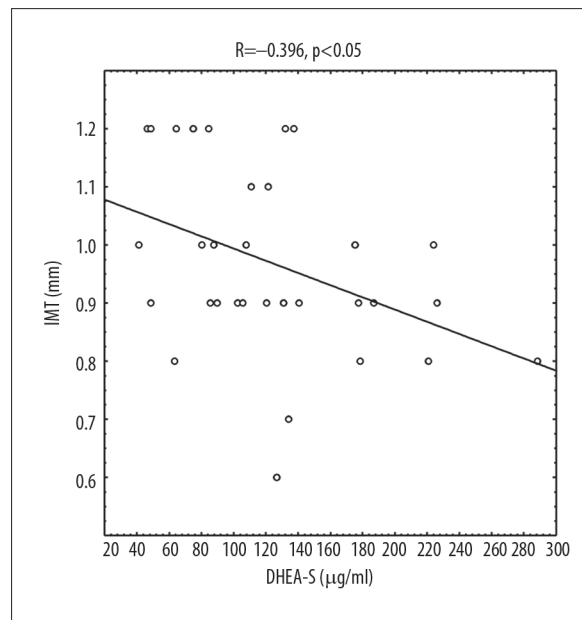
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Figure 4. Correlation between dehydroepiandrosterone sulfate (DHEA-S) concentration in plasma and thickness of intima-media complex (IMT) in right carotid artery in smoking postmenopausal women. R – Spearman's rank correlation coefficient.
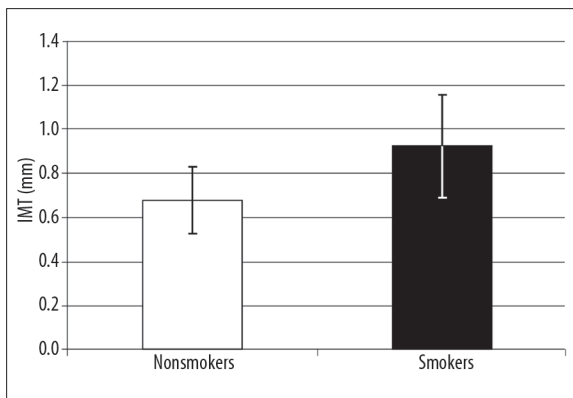

Figure 5. Thickness of intima-media complex (IMT) in carotid right arteries in smokers and nonsmokers in postmenopausal women. The bars represent mean (in mm) ± standard deviation (SD).

observations led us to the conclusion that chronic cigarette smoking can disrupt the arterial wall long before atherosclerosis is clinically manifested.

The IMT, greater in smokers, may be connected with increased activity of the adrenergic system. In this study, in the group of postmenopausal smoking women, we observed
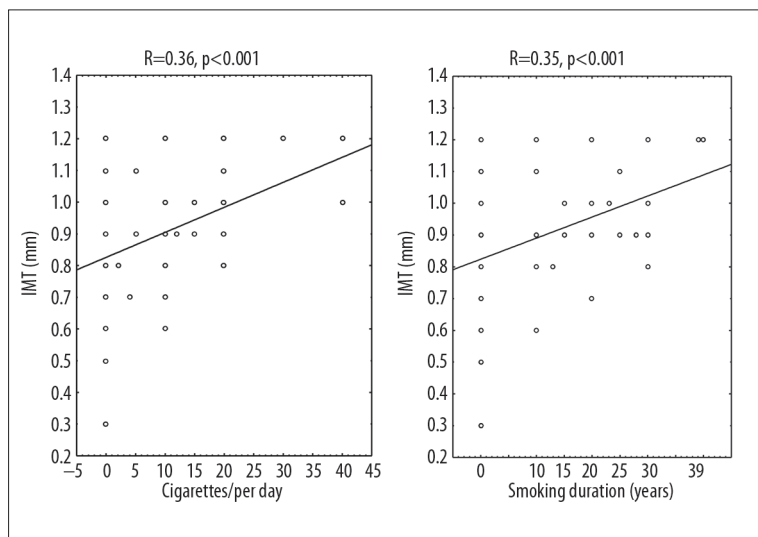

Figure 6. Correlation of cigarette smoking intensity and habit duration with the thickness of intima-media complex (IMT) in carotid right artery in smoking postmenopausal women. R – Spearman's rank correlation coefficient.

endothelium, demonstrating a significant negative correlation of endothelial dilatative function with IMT. The carotid IMT, used as a marker of generalized atherosclerosis, increases with age and the number of cardiovascular disease risk factors [11,42,43]. A significant correlation between carotid IMT and Framingham cardiovascular score was reported [44]. In our population of postmenopausal hypertensive women without clinically manifested symptoms of atherosclerosis we found a significantly greater IMT in the right carotid artery in smokers than in nonsmokers. The IMT correlated with the intensity of smoking and duration of the habit. Our data confirmed the results of several clinical studies that demonstrated smoking was associated with increases in IMT in peripheral arteries [45,46]. These

an increase in arterial blood pressure. It may therefore be concluded that IMT can also result from greater and more frequent increases in arterial blood pressure.

In the group of nonsmokers we observed higher mean values of fasting glucose and higher obesity indices as well as tendency to more frequent occurrence of metabolic syndrome. These results confirmed the well known relationship between cigarette smoking and fasting glucose in blood and body weight.

Associating smoking with fasting glucose is ambiguous [47]. Studies of some authors suggest an increase in fasting glucose levels in blood [48] and increased insulin resistance in smokers as a direct effect of the negative impact of nicotine on

peripheral glucose uptake [49] and reduction in insulin secretion [50]. Nicotine, stimulating the secretion of hormones acting opposite to insulin – catecholamines [51], growth hormone [52] and cortisol – may increase fasting glucose levels.

In the studies of Daniel et al. [53], a high activity of pancreatic beta cells in current nondiabetic smokers was observed as assessed by blood glucose, fasting insulin and HOMA, whereas the studies of Henkin et al. [54] showed no association between active smoking and the sensitivity of tissues to insulin.

In our studies the levels of fasting glucose were lower in current smokers compared with nonsmokers. The interpretation of this finding seems difficult and complex. The observed difference can be explained by the results of recent research by Mineur et al. in mice [55], demonstrating that the activation of hypothalamic α3β4 nicotinic acetylcholine receptors leads to activation of pro-opiomelanocortin neurons. Next, melanocortin 4 receptors are activated, which causes a decrease in food intake [55]. Therefore, nicotine, by influencing the hypothalamic melanocortic system and with the participation of synaptic mechanisms, reduces the intake of food, and thus may lower glucose levels and body weight in smokers.

It is known that smoking can contribute to appetite suppression and at the time of smoking cessation the appetite grows and weight gain appears. Interestingly, the increased adrenergic activity occurs not only in smokers but also in obese individuals and in patients with metabolic syndrome [56,57]. Both cigarette smoking and obesity are considered to be response to stress. Thus, it is likely that the clinical manifestation of arterial hypertension in postmenopausal women might depend on a different response to stress.

The inflammatory response is an essential component in the initiation and propagation of atherosclerosis [24]. Cigarette smoke and other well-known cardiovascular risk factors such as symptoms of the metabolic syndrome – obesity, lipid and carbohydrate disorders and arterial hypertension – initiate the inflammatory state in endothelium. Endothelial inflammation proceeds with the participation of coagulation and fibrinolysis, cytokines and inflammatory cells, adrenergic system stimulation, oxidation stress, endothelial metabolism disorders and its autocrine function [38,58–60]. Smoking may activate leukocytes, endothelial and vascular smooth muscle cells to produce matrix metalloproteinases, which are capable of degrading many extracellular matrix proteins. There is much evidence supporting an association between increased production of matrix metalloproteinases and the development of aortic aneurysms in smokers [24,61]. Moreover, cigarette smoking in women increases expression of inflammatory markers, including interleukin 6, C-reactive protein, E-selectin, P-selectin and intercellular adhesion molecule-1 [62].

There is a large body of evidence in the literature supporting the endothelial changes in smokers with coronary artery disease. They mainly concern the increased dynamics of the atherosclerotic process and destabilization of atheromatous plaque. In smokers with stable coronary artery disease, increased concentrations of interleukin 2 and sP-selectin in blood serum were reported. Nicotine activates inflammatory processes of the vascular wall, among others, through change in cytokines activity [63]. Damaged endothelium is the activation site of adhesive molecules, increased permeability for macromolecules and leukocyte adhesion, and increased synthesis of a number of chemotactic factors for monocytes and macrophages [58,64]. Cavusoglu et al. [58] suggested that in patients with coronary artery disease with no history of cardiac infarct cigarette smoking led to an increase in the amount of adhesive molecules (VCAM-1), which was the reason for acceleration of atherosclerotic progression. Studies of Kangavari et al. [13] concerning atherosclerotic plaque of carotid artery which was destabilized, revealed in smokers compared with nonsmokers increased macrophage immunoreactivity, increase in matrix enzyme activity (macrophage-derived metalloelastase - MMP-12), decrease in the activity of TIMP-1, and also decrease in elastin content, which may be evidence for the role of cigarette smoking in destabilization of atherosclerotic plaque.

It is hard to refer the study results of Kangavari et al. [13] concerning the destabilization of atherosclerotic plaque to the activity of plasma matrix metalloproteinases and inflammatory markers measured in our studied population of women in whom clinically manifested atherosclerosis was not observed. The activity of the inflammatory process assessed by the comparison of TNF-α, ICAM-1 concentrations and also matrix metalloproteinases (MMP-9, TIMP-1) in plasma of smokers and nonsmokers did not significantly differ. This might suggest low activity of inflammatory process dependent on cigarette smoking in patients without clinical symptoms of disease. Simultaneously, the results of our studies might confirm a minor relationship of chronic vascular changes with cigarette smoking compared with acute episodes of ischaemia described in the literature [13,19].

After menopause the influence of estrogens declines, whereas that of androgens increases. DHEA-S is a marker for adrenal DHEA, a weak androgen, known to exert protective effects against atherosclerosis [29,30,65]. In premenopausal women and in men, decreased serum levels of DHEA-S are associated with increased risk of coronary artery disease [66,67]. In postmenopausal women, DHEA-S was found to be more potently related to coronary artery disease and cardiovascular mortality than in men and premenopausal women (30, 68); however, there is a report showing lack of an association between DHEA-S and development of atherosclerosis in both men and women [69].

In the present study, we documented a negative correlation of plasma DHEA-S concentration with the size of IMT in the right carotid artery in smokers. Kanazawa et al. [30] observed in 106 postmenopausal women the relationship between the DHEA-S deficit and the development of vascular atherosclerosis assessed on the basis of IMT, independently of other coexisting risk factors such as age, BMI, and diabetes. In another study, involving 101 pre- and postmenopausal females, higher DHEA-S concentrations were related to lower carotid wall thickness; this relationship was independent of cardiovascular risk factors but was dependent on age [65]. Taken together with the described reports, our results support a role for endogenous DHEA-S in the development of atherosclerosis and may suggest that in smoking postmenopausal women normal DHEA-S levels may benefit the carotid artery wall.

CONCLUSIONS

1. In hypertensive postmenopausal women without clinically manifested symptoms of atherosclerosis, vascular changes

assessed on the basis of IMT measurements are more intense in smokers compared with nonsmokers and depend on the duration and intensity of cigarette smoking.

2. The clinical picture of arterial hypertension in the post-menopausal period seems to be 2-way: with simultaneous occurrence of metabolic syndrome elements in nonsmokers (obesity, increased fasting glucose levels in blood) or with higher values of arterial blood pressure and heart rate at daytime and night (with lower BMI and fasting glucose levels in blood) in smokers.

3. In smoking women higher values of arterial pressure and heart rate at daytime are observed as well as maintenance of the changes at night, which may result from long-term stimulation of the adrenergic system in smokers.

4. The duration and intensity of the smoking habit in women without clinically manifested symptoms of atherosclerosis does not influence the concentration of inflammatory markers (TNF-α, ICAM-1) or matrix metalloproteinases (MMP-9, TIMP-1) in plasma, which might suggest a different mechanism of cigarette smoking influence on progression of atherosclerosis.

5. Deficit of DHEA-S may have an adverse impact on the development of atherosclerotic changes in hypertensive postmenopausal women who smoke.

Acknowledgements

Study limitations

The results of our study need to be interpreted with caution due to various limitations. First, the sample size is not large enough to make any definite conclusions. Second, patients in this study had taken angiotensin converting enzyme inhibitors, angiotensin II receptor blockers and/or beta adrenergic receptors antagonists for hypertension treatment. We could not provide any insight on treatment implication and related outcome on using IMT measurements. Third, there are some evidence that angiotensin converting enzyme inhibitors are involved in downregulation of vascular wall inflammation [70], and we cannot exclude that these medications could affect plasma concentration of the measured inflammatory markers and metalloproteinases. However, study subgroups did not differ in antihypertensive treatment; thus their possible effect might be disregarded. The present study gives an impetus for the realization of further studies to elucidate the impact of cigarette smoking on endothelial function in women after menopause.

Disclosures

None

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