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Markers of endothelial dysfunction in patients with arterial hypertension exposed to occupational irradiation of low intensity

Aim	To study the association between concentrations of endothelial dysfunction (ED) markers and arterial hypertension (AH) in people who were exposed to long-term action of «low-dose» ionizing radiation.
Material and methods	The study subjects were men of middle age (45–55 years) who were workers of the Siberian Integrated Chemical Plant with the length of service on the shop floor of at least 5 years. The subjects were divided into the main group (n=96) consisting of workers with grade 1–2 AH and the control group (n=48) consisting of arbitrarily healthy workers. Both groups contained workers who had been exposed to long-term occupational low-intensity irradiation (γ-radiation) and those not exposed to this irradiation. The study evaluated risk factors for cardiovascular diseases, presence of concomitant diseases, blood biochemistry (concentrations of glucose, high-sensitivity C-reactive protein (hsCRP), total cholesterol, low-density lipoproteins, high-density lipoproteins, triglycerides, creatinine, and ED markers, including endothelin, angiotensin II, von Willebrand factor, C-type natriuretic peptide, tissue plasminogen activator, tumor necrosis factor α (TNF-α), and homocysteine, major clinical data, total dose of external irradiation, and the content of 239Pu in the body.
Results	AH was associated primarily with excessive body weight and severity of atherogenic dyslipidemia and homocysteinemia. Higher plasma concentrations of TNF-α and a tendency to increasing hsCRP in the AH group, as distinct from the control group of arbitrarily healthy men, indicated a proinflammatory shift. The ED markers were related with clinical data of AH patients and associated with the lipid profile and increased blood concentrations of inflammatory mediators. The radiation exposure did not change the ED marker array in AH patients, which did not allow recommendation of the studied plasma indexes for detection of vascular endothelial injury in workers with AH of the Siberian Integrated Chemical Plant.
Conclusion	The study results evidenced the absence of adverse effects of long-term occupational exposure to low-intensity radiation on the vascular endothelium as evaluated by ED markers. In men aged 45–55 years, AH was associated primarily with excessive body weight, homocysteinemia, and atherogenic dyslipidemia.

Keywords	Arterial hypertension; risk factors; "low" doses of ionizing radiation; endothelial dysfunction
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Introduction

The unsatisfactory control of cardiovascular diseases (CVDs) and the relevant risk factors (RFs) is the leading cause of negative medical and demographic processes caused by this group of diseases in the Russian population. The high CVD prevalence and significant social and corresponding economic losses require further development of early diagnosis methods, as well as the study and correction of RF not only for specific regions but also professional cohorts.

Personnel working in the nuclear industry are characterized by specific production activities, biological rhythm desynchronization, psychological stress, and other characteristics leading to the early onset of CVDs [1, 2].

In recent years, much attention has been paid to anthropogenic and technogenic factors in the development of CVDs. The contribution of technogenic radiation in the morbidity and mortality risk due to CVD has been actively discussed, taking into account the increased use of ionizing

radiation (IR) for industrial and medical purposes [1–7]. Endothelial dysfunction (ED) determines the CVD pathogenesis, and the detected vascular disorders can be reversible at its initial stage [8, 9].

There is still insufficient scientific knowledge which might enable a better understanding of the mechanisms of atherogenesis and arterial hypertension (AH) at small (less than 0.1 Sv) doses and a low IR dose rate.

The objective of the study was to investigate ED markers in patients with AH during prolonged exposure to small IR doses.

Material and methods

The study object was the personnel of the Siberian Chemical Combine (SCC), until recently one of the world's largest complex of nuclear industry facilities. In total the number of SCC personnel employed between January 1, 1950, to December 31, 1994, and who worked at the enterprise for at least three years, consists of 34,146 people, of whom 23,659 male. The observation period was from 1998 to 2018. Of the entire cohort, 6,334 male and 2,056 female subjects were individually monitored for external radiation. The range of external radiation doses of male employees of SCC included in the analyzed cohort was 0.04–1,685.16 mSv (median 21.22 mSv, interquartile range 3.8–88.05).

The study protocol complies with the Declaration of Helsinki, stating ethical principles for medical research involving human subjects, and was approved by the local ethics committee of the Seversk Biophysical Research Center of FMBA of Russia. All patients included in the study signed the informed consent form.

The study included middle-aged male subjects (45–55 years old) with at least five years of experience in SCC main production. The study group (n=96) was formed by employees with stage 1–2 AH, and the control group (n=48) included conditionally healthy employees without CVDs. Both groups included employees who were exposed to long-term low-intensity occupational radiation (gamma radiation) and employees who were not exposed to radiation. The study group's inclusion criteria were an age of 45–55 years and less than 5 years of AH. Exclusion criteria: high and accelerated AH; clinically significant coronary or peripheral atherosclerosis; history of acute vascular complications; heart failure above stage I; and severe somatic diseases.

The mean age of male subjects in the study group was 49.8±2.9 years, service duration in SCC varied from 7 to 25 years (on average, 18.7±2.6 years). The duration of hypertension was 2.6 (1.8; 3.2) years. The mean age of male subjects in the control group was 49.7±3.8 years, and the number of years in SCC was between 6 to 24 years (mean18.2±2.3 years).

AH was diagnosed based on the European Society of Cardiology Guidelines (2018) [10]. The duration of AH was reconfirmed from medical records. Body mass index (BMI) ≥25 kg/m^2 was considered overweight, obesity was diagnosed at BMI≥30 kg/m^2, and waist circumference (WC) was measured in centimeters. The smoking status, positive family history, and diabetes mellitus were checked with medical documentation. The level of psychological stress was estimated using the Reeder test (1969) [11].

Contact with IR sources was clarified retrospectively (after inclusion in the study) based on the individual dosimetric control data. 50 (52.1%) and 46 (95.8%) subjects were exposed to IR in the study and control groups, respectively. The total external exposure dose (TEED) was 19.6 [12.2; 36.4] mSv and 22.3 [15.1; 49.2] mSv in the study and control groups, respectively ($p>0.05$). ^{239}Pu levels were determined in the body by a calculation based on a biophysical study of 24-hour urine volume, while values of the estimated parameter were at a minimum level.

All studies were conducted in drug-free conditions. The majority of SCC employees with AH (70%) did not use medications. For the rest (30%), antihypertensive therapy was discontinued three weeks before the examination.

Dyslipidemia was diagnosed with the following lipid spectrum abnormalities: total cholesterol (TC) >4.9 mmol/L (190 mg/dL) and/or low-density lipoprotein (LDL); cholesterol >3.0 mmol/L (115 mg/dL) and/or high-density lipoprotein (HDL) cholesterol <1.0 mmol/L (40 mg/dL); and/or triglycerides (TG) >1.7 mmol/L (150 mg/dL). The atherogenic index was calculated automatically. In order to assess renal filtration function, the glomerular filtration rate was calculated using the MDRD formula. Fasting hyperglycemia as an RF of CVD was observed with plasma glucose levels of 5.6–6.9 mmol/L. The reference values for high-sensitivity C-reactive protein (hs-CRP) were 0–5 mg/dL.

The diagnostic and treatment laboratory of Tomsk National Research Center for Medicine by the Russian Academy of Sciences assessed plasma concentration of the following markers of ED using ELISA: endothelin; angiotensin II; von Willebrand factor; C-type natriuretic peptide (CNP); tissue plasminogen activator (t-PA); tumor necrosis factor-α (TNF-α); and homocysteine. Reference values of endothelin were up to 5 fmol/mL; angiotensin II – 10–60 pg/mL; von Willebrand factor 0.5–1.5 U/mL; CNP – 2–3 pmol/L; t-PA – 2–8 ng/mL; TNF-α – 0–8.1 pg/mL; and homocysteine – 5–15 mμmol/L.

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The arithmetic means and standard deviations (M±SD) were calculated for quantitative indicators with the normal distribution. When the distribution was non-normal, the median and the lower and upper quartile (Me [LQ; UQ]) were used.

The correlation between the discrete, qualitative indicators was studied using the analysis of two-dimensional contingency tables and the calculation of χ^2 and the φ coefficient, to characterize the strength of correlation between two qualitative indicators. The Pearson correlation coefficient was also used. When the distribution was non-normal, parameters were compared using non-parametric criteria: the Kruskal–Wallis one-way analysis of variance; median test; and the Spearman rank correlation coefficient. The logistic regression method in SPSS 10.0.5 (SPSS Inc., USA) was used for the multivariate analysis. When testing statistical hypotheses, the critical significance level (p) was taken to be 0.05.

Results

ED can be defined as the inadequate (increased or decreased) formation of various biologically active substances in the endothelium. One of the methods for assessing the severity of ED is to assess these substances' blood concentration.

Table 1. ED markers in patients of the study and control groups

Parameter	Study group (n=96)	Control group (n=48)
Glucose, mmol/L	6.15±0.64*	5.84±0.53
GFR, mL/min/1.73m^2	99.76±28.51	89.88±19.50
TC, mmol/L	6.08±1.03	5.79±0.84
LDL, mmol/L	4.02±0.78	3.93±0.77
TG, mmol/L	2.05±0.41*	1.21±0.38
HDL, mmol/L	1.06±0.21*	1.2±0.22
CNP, pmol/L	3.41±1.03	3.6±0.97
von Willebrand factor, units/mL	0.75±0.09	0.74±0.10
Angiotensin II, pg/mL	76.97±7.53	76.69±6.33
Creatinine, μmol/L	100 [93.5; 112]	98.5 [90.0; 106]
hs-CRB, mg/dL	3.83 [1.59; 7.43]	1.91 [1.28; 5.95]
Endothelin, fmol/mL	1.45 [0.68; 3.07]	1.5 [0.58; 2.66]
TNFα, pg/mL	0.55* [0.047; 1.24]	0.178 [0.02; 0.53]
Homocysteine, μmol/L	8.77* [7.32; 12.26]	7.33 [6.13; 9.05]
t-PA, ng/mL	1.77* [1.21; 2.42]	1.25 [0.92; 2.094]
Atherogenicity index	4.46* [3.67; 5.54]	3.65 [3.15;4.68]

*, statistically significant differences between the study and control groups (p < 0.05). GFR, glomerular filtration rate; TC, total cholesterol, LDL, low-density lipoprotein, HDL, high-density lipoprotein, TG, triglycerides, CNP, C-type natriuretic peptide, hs-CRP, high-sensitivity C-reactive protein, TNFα, tumor necrosis factor α, t-PA, tissue plasminogen activator.

One of our studies found that patients with AH who had a dose load in comparison with the conditionally healthy employees of SCC exposed to radiation during their professional activities, were characterized by a high prevalence of abdominal obesity (χ^2=5.95; p=0.015) and hypertriglyceridemia (χ^2=16.94; p=0.0003). Patients with AH tended to have a higher pulse wave velocity and higher left ventricular mass index than conditionally healthy male subjects [12].

At the first stage of the study, parameters were compared in the study and control groups. In this study, unlike conditionally healthy individuals, patients with AH showed increased levels of homocysteine, TG, and decreased plasma HDL cholesterol, as well as a tendency towards LDL cholesterol increase with comparable values of TC (Table 1). Blood glucose levels in patients with AH did not exceed the reference values but were higher than in the control group. Increased levels of TNF-α and a tendency towards higher levels of hs-CRP in patients with AH when compared with conditionally healthy employees of SCC showed the presence of pro-inflammatory shifts in the patients studied. The von Willebrand factor plasma levels did not differ in the study and control groups. The t-PA levels exceeded the reference values in the conditionally healthy employees of SCC and were lower than in patients with AH (Table 1).

Correlation analysis showed that systolic blood pressure (BP) is associated with increased plasma levels of TNF-α (rs=0.41; p=0.00009) and homocysteine (rs=0.27; p=0.013). Diastolic BP in patients with AH had weak direct correlations with the atherogenic index (rs=0.16; p=0.034) and plasma levels of homocysteine (rs=0.27; p=0.011) and angiotensin II (rs=0.26; p=0.015). For systolic and diastolic BP, positive correlations were found with anthropometric parameters: systolic BP with BMI (rs=0.18; p=0.03) and WC (rs=0.24; p=0.032); diastolic BP with BMI (rs=0.18; p=0.03) and WC (rs=0.24; p=0.032). Pulse BP value was associated with TNF-α (rs=0.47; p<0.00001), homocysteine (rs=0.37; p=0.001) and hs-CRP (rs=0.22; p=0.043) plasma concentration. WC was associated with the main lipid spectrum parameters, most significantly with TG (rs=0.53; p=0.002) and the atherogenic index (rs=0.48; p=0.002).

With a longer duration of AH, TNF-α (rs=0.37; p=0.001) and homocysteine levels (rs=0.32; p=0.003) increased. The hs-CRP levels correlated with TNF-α (rs=0.23; p=0.035) and anthropometric parameters: BMI (rs=0.37; p=0.0004); and OT (rs=0.35; p=0.001). Homocysteine plasma levels had a direct correlation with the levels of TNF-α (rs=0.45; p=0.00001), von Willebrand

factor (rs=0.35; p=0.001), and angiotensin II (rs=0.44; p=0.00002). Plasma t-PA was strongly associated with anthropometric parameters: BMI (rs=0.46; p < 0.00001); WC (rs=0.51; p=0.000001); and weakly correlated with pulse pressure (PP) (rs=0.32; p=0.003). t-PA was moderately inversely correlated with the atherogenic index (rs=–0.41; p=0.00008).

The second stage of the study involved a comparison of patients with AH with a dose load (a radiation load subgroup) and those without (a no-radiation load subgroup). Patients in the study groups with AH did not differ significantly in terms of the frequency and severity of changes in the arteries (sphygmography), or the structural and functional parameters of the heart (echocardiography) [12]. The frequency of dyslipidemia, obesity, and fasting hyperglycemia was comparable in the subgroups. Table 2 shows the biochemical plasma parameters studied, depending on the dose load in the studied SCC employees. In this study, the plasma levels of ED did not differ in the subgroups compared. The only difference was high HDL cholesterol levels and a lower atherogenicity index in employees with a dose load.

In the correlation analysis, the value of TEED was correlated with the levels of HDL cholesterol (rs=0.38; p=0.0002) and CNP (rs=0.38; p=0.0003) in patients with AH with a dose load. Plasma hs-CRP correlated with the amount of 239Pu (rs=0.24; p=0.027). Plasma endothelin was weakly correlated with 239Pu (rs=–0.23; p=0.03) and age (rs=0.22; p=0.044). Systolic and diastolic BP levels were associated with TEED accumulation rate (rs=0.22; p=0.008; rs=0.22; p=0.008, respectively).

Logistic regression analysis was used to determine the association of CVD RFs with AH at 45–55 years. The statistical model included: anthropometric characteristics; age; level of psychological stress; sphygmometry parameters; blood lipid spectrum; atherogenic index; levels of hs-CRP and ED markers; as well as exposure characteristics of technogenic radiation (exposure history, TEED). Table 3 presents the results of multivariate analysis of the correlation of the analyzed RF with the presence of AH.

AH in middle-aged male subjects (45–55 years) was associated with BMI (p=0.009), plasma homocysteine (p=0.015), plasma atherogenicity (p=0.015), and pulse wave velocity (p=0.167). The predictive accuracy of the resulting model was 73.6% with good specificity (82.5%). The ED markers studied were not associated with AH in male individuals aged 45–55 years. The technogenic radiation parameters were also not associated with AH in the examined SCC personnel.

The study was limited by its small sample size and non-use of ultrasound diagnostics to confirm ED. Further observation of SCC employees is being continued, in order to determine the predictor significance of the used ED markers.

Table 2. ED markers in the study group based on radiation exposure

Parameter	No exposure (n=46)	Exposure (n=50)
Glucose, mmol/L	5.96±0.54	6.12±0.72
GFR, mL/min/1.73m^2	97.37±26.2	92.45±25.24
TC, mmol/L	5.92±0.96	5.96±0.93
LDL, mmol/L	3.95±0.76	3.94±0.85
TG, mmol/L	1.62±0.25	1.59±0.38
HDL, mmol/L	1.03±0.25	1.21±0.24*
CNP, pmol/L	3.35±0.92	3.61±1.05
von Willebrand factor, units/mL	0.71±0.13	0.72±0.12
Angiotensin II, pg/mL	73.66±6.61	81.13±7.09
hs-CRB, mg/dL	2.88 [1.28; 7.23]	3.45 [1.49; 7.52]
Endothelin, fmol/mL	1.48 [0.62; 2.4]	1.43 [0.60; 3.86]
TNFα, pg/mL	0.37 [0.03; 0.84]	0.29 [0.015; 0.68]
Homocysteine, μmol/L	8.63 [6.54; 11.40]	7.76 [6.81; 9.69]
t-PA, ng/mL	1.63 [1.26; 2.15]	1.21 [0.78; 2.49]
Atherogenicity index	4.64 [3.39; 5.38]	3.87* [3.11; 4.52]

*, statistically significant differences between the subgroups (p < 0.05). GFR, glomerular filtration rate; TC, total cholesterol, LDL, low-density lipoprotein, HDL, high-density lipoprotein, TG, triglycerides, CNP, C-type natriuretic peptide, hs-CRP, high-sensitivity C-reactive protein, TNFα, tumor necrosis factor α, t-PA, tissue plasminogen activator.

Discussion

The mechanisms of atherogenesis and AH caused by technogenic radiation, especially at small doses and a low rate of IR, are still not clear. CVDs are the most likely stochastic effect of radiation exposure [1–7]. The presence of special cellular epigenetic effects of IR in low-renewing tissues (endothelium and vascular wall myocytes) has been actively discussed in recent years [13]. Endothelium damaging factors include: hypercholesterolemia and hypertriglyceridemia; hyperhomocysteinemia; increased proinflammatory cytokine concentration; and possibly IR [8, 9]. For the first time, the ED marker range was assessed in patients with AH exposed to low-rate occupational radiation.

AH in the employees of SCC examined here is accompanied by alterations in some of the studied plasma biochemical parameters. For example, the patients with AH

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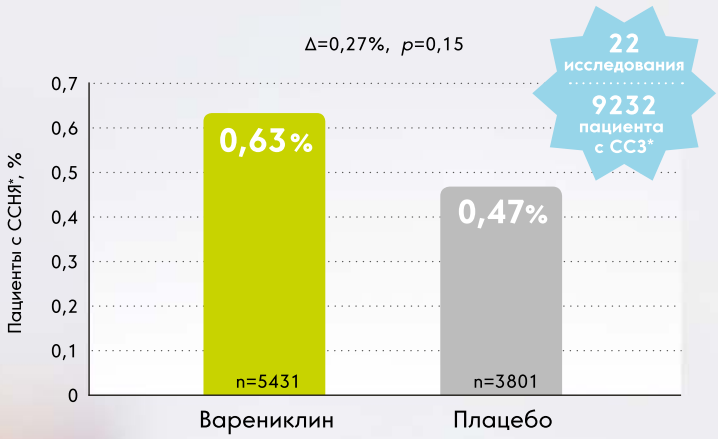

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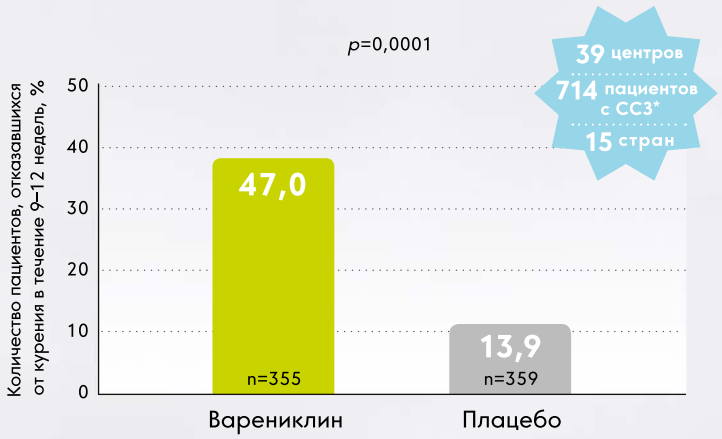
ЭФФЕКТИВНОСТЬ ЧАМПИКСА У ПАЦИЕНТОВ С СЕРДЕЧНО-СОСУДИСТОЙ ПАТОЛОГИЕЙ[3]



- В исследовании принимали участие курящие пациенты с высокой степенью тяжести никотиновой зависимости **с диагностически подтвержденной сердечно-сосудистой патологией**; диагноз поставлен не менее чем за 2 месяца до начала исследования.
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1. Инструкции по применению лекарственного препарата для медицинского применения Чампикс® от 10.06.2019. ЛСР-006439/08-100619.
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*CC3 – сердечно-сосудистые заболевания.

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Table 3. Multi-way analysis of the correlation between RFs and the presence of AH in employees of SCC

Risk factors	Beta coefficient	Standard error	Wald factor	Significance level
BMI, kg/m^2	0,147	0,056	6,881	0,009
Atherogenicity index	0,834	0,343	5,928	0,015
Homocysteine, μmol/L	0,205	0,084	5,922	0,015

BMI, body mass index.

studied here have increased hs-CRP and ED markers (homocysteine) in plasma, when compared with conditionally healthy SCC employees, as well as hypertriglyceridemia and hypoalphacholesterolemia.

The glucose level in patients with AH was significantly higher than in conditionally healthy SCC employees. There were no changes in the endothelium hemostatic function (t-PA, Von Willebrand factor) in the examined SCC employees. In terms of the humoral regulation of vascular tone (endothelin, angiotensin II, CNP), vasoconstrictor and vasodilating effects were balanced in both patients with AH and conditionally healthy employees contacting with IR sources. In general, the studied ED markers spectrum shows inflammation in the inner lining of blood vessels. This develops in response to the damaging effects of toxic factors and existing metabolic disorders.

A study of the correlations between AH and individual conventional RFs in SCC personnel established well-known associations with hypertriglyceridemia (χ^2=16.94; p=0.0003) and obesity (χ^2=5.95; p=0.015) were found. Abdominal obesity, insulin resistance, and homocysteinemia play significant roles in the AH pathogenesis in middle-aged male subjects (45–55 years). ED is an essential element in developing the blood vessel wall inflammation (increased hs-CRP, TNF-α) in the SCC employees examined here, followed by an increase in its stiffness.

There were no significant changes in the biochemical plasma markers studied in male patients with AH exposed to long-term low-rate IR. No stenotic lesions of arterial vessels were found in the examined SCC employees [12]. This may be due to the protective effect of small doses of IR on the vascular wall and short disease duration. Assessment of the ED markers profile in persons with contact with technogenic radiation sources did not reveal adverse effects of IR (γ-radiation <0.1 Sv) on the part of the cardiovascular system studied here.

With the progression of AH, the renin-angiotensin-aldosterone system is activated even more, and there is an imbalance between vasodilating, antithrombotic, and vasoconstrictor, proatherogenic regulatory mechanisms with a predominance of the latter [10]. In this case, short-lived endogenous peptides are no longer able to compensate for the resulting endothelial damage. It is important to note that the release of proteins from endotheliocytes is controlled through RNA activation, and the IR effect on the genome has been proven [14].

Initial changes in cardiovascular and renal function associated with AH will also affect the plasma levels of biochemical ED markers.

In persons exposed to occupational radiation, the plasma atherogenic index is lower, and accompanied by a tendency towards a decrease in plasma TNF-α. With the increased protective effect of HDL cholesterol, the damaging effect of toxic factors present in metabolic disorders decreases. The value of TEED had direct correlations with HDL cholesterol and vasodilating CNP plasma concentrations. With prolonged exposure to small doses of IR, hormesis may manifest as the decreased atherogenic and vasoconstrictor potential of the plasma. However, it is impossible to completely exclude the genetic heterogeneity of the compared employee groups, given the association of HDL levels with the favorable anti-atherogenic family history [10].

Conclusion

The blood levels of biologically active substances act as biomarkers not only of target organ damage in AH (heart or renal failure), but also show the existence of early-stage ED. Assessment of the vascular wall endothelium state in individuals exposed to occupational technogenic radiation when performing their professional duties did not reveal the adverse effects of IR (gamma radiation) on the levels of ED markers in the studied dose range (0–0.1 Sv). The study was limited by its small sample size and unrecorded interfering factors which could impact on the result. AH in male subjects aged 45–55 years is mainly associated with overweight, the severity of atherogenic dyslipidemia and homocysteinemia. Increased levels of hs-CRP and TNF-α, reflecting a proinflammatory shift in the endothelium, is an early symptom of emerging vascular disorders in AH.

No conflict of interest is reported.

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