ORIGINAL ARTICLE

Assessment of selected serum inflammatory markers of acute phase response and their correlations with adrenal androgens and metabolic syndrome in a population of men over the age of 40

Waldemar A. Herman[1], Aleksandra Seńko[2], Izabela Korczowska[3], Katarzyna Łącka[4]

1 HERMED Outpatient Endocrinology Clinic, Wschowa, Poland
2 Student Scientific Club, Poznan University of Medical Sciences, Poznań, Poland
3 Department of Clinical Immunology, Poznan University of Medical Sciences, Poznań, Poland
4 Department of Endocrinology and Metabolism, Poznan University of Medical Sciences, Poznań, Poland

KEY WORDS

α_1-antichymotrypsin, adrenal androgens, aging men, C-reactive protein, transferrin

ABSTRACT

INTRODUCTION Inflammatory mechanisms and decreasing adrenal androgen production are involved in the pathogenesis of numerous age-related diseases.

OBJECTIVES The aim of our study was to assess selected negative (transferrin) and positive (α_1-antichymotrypsin [α_1-ACT], C-reactive protein [CRP]) acute phase proteins, and to investigate associations between these proteins and serum dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) levels, as well as anthropometrical and biochemical indices of metabolic syndrome (MS) in men over 40 years of age.

PATIENTS AND METHODS In 271 randomly selected men aged 40 to 80 years and living in the province of Lubuskie, Poland, transferrin, α_1-ACT, CRP, and adrenal androgens were measured and features of metabolic syndrome were evaluated.

RESULTS Age is strongly correlated with acute phase proteins in men: positively for CRP and α_1-ACT ($r = 0.216$, $P < 0.001$ and $r = 0.193$, $P < 0.05$, respectively) and negatively for transferrin ($r = -0.268$, $P < 0.0001$). CRP revealed a negative correlation with DHEA ($r = -0.248$, $P < 0.05$), although not with DHEA-S. There were no correlations between α_1-ACT, transferrin, and adrenal androgens. As opposed to adrenal androgens, serum CRP and transferrin (but not α_1-ACT) levels are associated with metabolic syndrome (MS) in men over 40 years of age ($P < 0.001$).

CONCLUSIONS A prognostic test using systemic markers of general inflammation (especially CRP) may help (as opposed to DHEA and DHEA-S) identify men over 40 years of age who suffer from MS.

Correspondence to:
Waldemar A. Herman, MD, Poradnia Endokrynologiczna „HERMED", ul. Zielona 8, 67-400 Wschowa, Poland, phone: +48-65-540-34-27, fax: +48-65-540-34-27, e-mail: wherman@wschowa.com.pl
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INTRODUCTION Cardiovascular events are considered to be the consequence not only of lipid disorders but also of low-grade chronic inflammation.[1] Recently, hypercholesterolemia and inflammation have been described as "partners in crime".[2]

The term "acute phase reactants" was introduced in 1941 by Avery and McCarthy.[3] An acute phase response is an early and nonspecific reaction of the body to disturbances in homeostasis caused by such factors as bacterial infections, inflammation, injury, combustion, cancer growth, and tissue ischemia leading to necrosis.

Clinical manifestations of these processes include an increase in leukocyte count and stimulation of acute phase protein and cell adhesion molecule production. Most of them rise during inflammation (positive acute phase serum proteins): haptoglobin, serum amyloid P

(SAP), β-fibrinogen, α_1-glicoprotein, C-reactive protein (CRP), α_1-antichymotrypsin (α_1-ACT), α_1-antitripsin, ceruloplasmin, and the complement component 3 factor. Their synthesis in the liver is stimulated mainly by proinflammatory cytokines: interleukin 6 (IL-6), interleukin 1, and tumor necrosis factor (TNF), which increase manifold in response to infection and tissue damage.[4] The main function of this reaction is to restore a disturbed physiological course of action.

It has been established that during the acute phase response and especially during chronic inflammatory diseases, plasma concentrations of transferrin, α_1-lipoprotein, transthyretin (prealbumin), fibronectin, transcortin, retinol-binding protein, and albumin are decreased, and they are therefore classified as negative acute phase proteins.[5]

CRP was discovered in 1930 by William Tillet and Thomas Francis, who first described the properties of serum containing CRP obtained from patients with severe fever and suffering from pneumonia.[6]

CRP (molecular weight of about 120 kDa) belongs to pentraxins, and similarly to SAP, it is built of 5 basically identical subunits. Its name originates from its ability to connect to the C-polysaccharide of the *Pneumococcus pneumoniae* bacterial wall. CRP activates the classical complement pathway and has opsonin activity.[7] Because of a short circulatory half-life (5–7 h), the serum CRP level depends only on its *de-novo* synthesis. That is why CRP is considered as a very sensitive indicator of inflammation. There is no direct correlation between CRP and the erythrocyte sedimentation rate.

One of the most important serine-protease inhibitors of serpin family, α_1-ACT, can even increase 5-fold during infection.[8] It is involved in the processes of coagulation and fibrinolysis and may play an important role in the development of vascular incidents.[9]

The main physiological role of transferrin is transportation of iron (Fe^{3+}) to the bone marrow. The serum transferrin level is increased in sideropenia but decreased in chronic inflammatory and neoplastic diseases. Men over the age of 70 have about 15% higher iron levels and transferrin saturation than women.[10]

Many studies have demonstrated positive correlations between low-grade inflammation and a decline in health of the elderly population.

Numerous previous studies have shown that inflammation is related to atherosclerosis. Inflammation initiates plaque formation, and then promotes its progression and rupture. In both men and women, intima-media thickness increased with elevated CRP levels. In men, but not in women, carotid luminal diameter was enlarged significantly with increasing CRP.[11] CRP levels were significantly higher in clinically unstable patients with neurological symptoms and a positive hyperintense magnetic resonance imaging signal caused by carotid intraplaque hemorrhage, a marker of atheroma instability.[12]

Low-grade inflammation with elevated CRP levels is correlated with aortic stiffness and acceleration of pulse wave velocity.[13] On the other hand, CRP is not correlated with the coronary calcium score in spiral computed tomography.[14]

Recently, there has been much interest in associations between inflammation and the metabolic status of elderly people.[15] It is widely known that CRP increases during aging in both sexes.[16] CRP is strongly related to many risk factors for cardiovascular diseases, including smoking and chronic somatic disorders.[17] The CRP level is also connected with coagulation factors (VIIc, IXc, Xc, and fibrinogen), diabetes status, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol (negative), and triglycerides (TAGs).[18] In addition, high-sensitivity CRP (hs-CRP) has been reported to have a positive correlation with atherosclerosis, although not independently of conventional risk factors.[19]

It seems that one of the common epidemiological factors of those diseases is adrenal androgen deficiency, which increases with age. The production of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) is 1% to 2% lower each year from the age of 25. This results in a decline of the body's immune status, which promotes atherosclerosis as well as neoplastic and autoimmune diseases.[20]

There is a likely association between a decreased adrenal androgen level in serum and chronic inflammatory diseases.

The aim of our study was to assess selected negative (transferrin) and positive acute phase proteins (α_1-ACT and CRP) and to investigate associations between these proteins and serum levels of adrenal androgens (DHEA, DHEA-S), as well as anthropometrical and biochemical indices of metabolic syndrome (MS) in men over 40 years of age.

PATIENTS AND METHODS Subjects living in the south-western region of Poland (Lubuskie province) and born in 1962, 1952, 1942, 1932, and 1922 were recruited by sending 632 invitation letters. This method allowed us to assess 275 (43.5%) positive answers.

Patients with hormonal disturbances of hypophysis-gonadal and pituitary-adrenal axis were excluded, including 1 man who had undergone surgical treatment for craniopharyngioma with a partial hypophysis insufficiency, and 3 men undergoing pharmacological therapy for prostatic cancer with analogous of the gonadoliberins.

Finally, the study comprised 271 men (50, 55, 56, 58, and 52 subjects aged 40, 50, 60, 70, and 80 years, respectively), living in small towns (n = 178, 65.68%) and in rural areas (n = 93, 34.31%).

Men with acute infections were temporarily excluded and again examined a few weeks later after they had recovered.

All study subjects completed a questionnaire which included questions about their marital and family status, occupation, work activity and professional hazards, exposure to risk factors, habits, past and current diseases, present use of medications, symptoms of androgen insufficiency, and a family history.

The smoking rate was estimated using the Brinkmann index (calculated by multiplying the number of smoking years and the number of cigarettes smoked per day).[21]

Physical examination included a complete general practice examination and assessment of possible symptoms of hypogonadism. Selected anthropometrical measurements were performed including the Quetelet's index (body mass index [BMI]) and waist circumference at the umbilicus level or at the level of maximum circumference.

MS was diagnosed according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria.[22]

Blood samples were collected in the morning after 12-hour fasting. The samples were immediately centrifuged and frozen until the assay.

The total cholesterol concentration was measured by enzymatic methods with esterase and cholesterol oxydase (the Cobas Integra set, Roche Company), the HDL concentration was measured using direct methods without precipitation, and TAGs using methods with phosphoglicerol oxydase and of hydrogen peroxide. The LDL concentration was calculated using the Friedewald formula, when the TAG level was below 400 mg%.

The serum levels of acute phase reactants α_1-ACT and transferrin were measured by rocket immunoelectrophoresis (LKB Multiphor System analyzer, Pharmacia, United States), using a method first described by Laurell.[23] Serum CRP levels were determined using high-sensitivity immunoassays (ELISA) – specific antibodies are used – produced by BioCheck, United States, and performed according to the manufacturer's instructions.

The lower limit of detection for CRP was 0.05 mg/l. The normal ranges for α_1-ACT, transferrin, and hs-CRP were 200 to 650 mg/l, 2000 to 3600 mg/l, and below 5 mg/l, respectively (for 95% confidence).

DHEA/DHEA-S levels were measured by the immunoenzyme method ELISA (Biosource-Company, Belgium), using ELX 800 analyzer (BIO-TEK, Instruments, Inc., Vermont, United States) with a sensitivity ≤0.1 ng/ml for DHEA (normal range 1.8–12.5 ng/ml), and ≤0.02 μg/ml for DHEA-S (normal range 1.0–4.2 μg/ml) for the 95% confidence range.

All samples were measured in duplicate and the averages were calculated.

Statistical analyses were conducted using SPSS software for Windows. All the studied parameters are expressed as mean values, followed by one standard deviation. Variables, which are not characterized by normal distribution, were analyzed using the Mann-Whitney and Kruskal-Wallis nonparametric tests for independent samples. The associations were estimated using the nonparametric Spearman rank correlation test. A $P < 0.05$ was considered statistically significant. The correlations were corrected for outliers (values that lie 1.5 interquartile range beyond the upper or lower quartile). Logic regression was used to estimate the odds ratios (OR) and a 95% confidence interval (CI) for the presence of discrete risk factors of androgen deficiency.

RESULTS General data analysis for acute phase proteins and adrenal androgens The measured values of α_1-ACT, CRP, and transferrin, in addition to serum adrenal androgen levels are presented in TABLE 1.

Serum acute phase protein levels in particular age groups with estimated correlation coefficients are demonstrated in the FIGURE.

The results have shown a strong negative correlation of both adrenal androgens with age ($r = -0.495$, $P < 0.001$ for DHEA, and $r = -0.551$, $P < 0.001$ for DHEA-S).

The serum α_1-ACT level was correlated with CRP ($r = 0.431$, $P < 0.0001$). No correlations were observed between transferrin and CRP, or between transferrin and α_1-ACT.

TABLE 1 Serum levels of acute phase proteins and adrenal androgens depending on age

Age (years)	Number of patients	hs-CRP (mg/l)	α_1-ACT (mg/l)	Transferrin (mg/l)	DHEA (ng/ml)	DHEA-S (μg/ml)
40	50	2.12 (±3.66)	373.92 (±131.09)	2873.60 (±702.58)	16.07 (±5.28)	1.842 (±1.06)
50	55	3.71 (±7.52)	389.55 (±108.53)	3313.38 (±974.49)	13.121 (±4.93)	1.286 (±0.64)
60	56	4.43 (±12.14)	406.82 (±157.68)	2673.80 (±600.49)	12.015 (±5.94)	1.039 (±0.55)
70	58	3.31 (±3.36)	400.38 (±110.04)	2670.17 (±728.81)	10.005 (±4.54)	0.799 (±0.48)
80	52	4.53 (±9.55)	411.10 (±165.04)	2506.90 (±570.77)	7.647 (±3.33)	0.648 (±0.36)

Abbreviations: α_1-ACT – α_1-antichymotrypsin, DHEA – dehydroepiandrosterone, DHEA-S – dehydroepiandrosterone sulfate, hs-CRP – high-sensitivity C-reactive protein

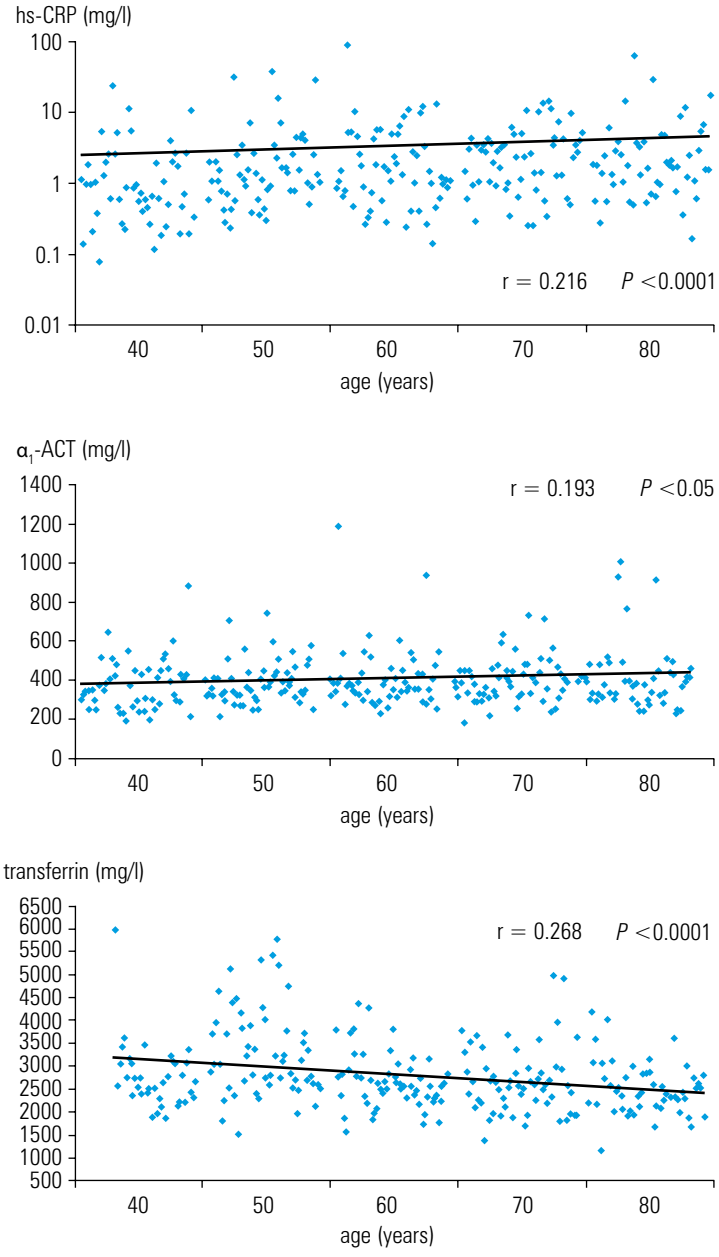

FIGURE Serum hs-CRP levels in particular age groups and their correlations with age
Abbreviations: see TABLE 1

Correlations between acute phase proteins and adrenal androgens CRP classification by tertiles (<1.0, 1.0–3.0, 3.0–9.9, and >9.9 mg/l), independent of age, is shown in TABLE 2.

The differences show a statistical significance between the groups of the lowest and highest concentrations of CRP serum levels in the domains of DHEA (r = –0.248, P <0.05), but not of DHEA-S.

The results have not shown any relationships between α_1-ACT accompanied by transferrin and both adrenal androgens.

Correlations between acute phase proteins and metabolic syndrome as well as cardiovascular diseases Eighty (29.52%) patients fulfilled the criteria for MS. It was observed in selected individuals in particular age groups: 8 (16.0%) patients in their 40s, 14 (25.45%) patients in their 50s, 22 (39.29%) patients in their 60s, 22 (37.29%) patients in their 70s, and 14 (26.92%) patients in their 80s.

TABLE 3 presents correlations between acute phase proteins and features of MS in conjunction with cigarette smoking.

A waist circumference above 102 cm (determined visceral deposition of fat tissue) was positively correlated only with CRP (r = 0.258, P <0.0001). No correlation was shown for α_1-ACT, or for transferrin and anthropometric measurements (BMI, waist circumference, waist-to-hip ratio).

Elevated blood pressure and serum TAG levels were not only correlated with α_1-ACT.

The results of a multivariate logistic analysis of the features associated with elevated CRP are presented in TABLE 4. Statistically significant correlations were revealed between increased CRP levels and the following previously diagnosed diseases:

1 coronary artery disease (P <0.005)
2 peripheral perfusion disturbances (P <0.01)
3 stroke in the past (P <0.01)
4 metabolic syndrome according to the NCEP criteria (P <0.001)

Transferrin (contrary to α_1-ACT) was also shown to be negatively correlated with the occurrence of MS (OR = 0.862, 95% CI 0.467–0.971%).

DISCUSSION Our study have shown that age is strongly and positively correlated with acute phase proteins in men, which had been previously confirmed in other studies.[24] However, global systemic iron reserve (not evaluated in our study) may significantly affect serum transferrin concentration.

It has been suggested that an increase in CRP associated with aging is connected mainly to the age-related rise of IL-6, which regulates the production of acute phase proteins and their release by hepatocytes.

Our study provides data on the associations between elevated acute phase proteins and selected common diseases in elderly patients. We demonstrated an increased level of acute phase proteins for patients with previously diagnosed ischemic heart disease, peripheral perfusion disturbances, and an episode of brain stroke (TABLE 4). This relationship would probably have been more visible, if we had conducted longitudinal studies.

The mechanism through which, in healthy individuals, even moderately elevated CRP (but within the normal range) plays the role of a predictive factor in progress of atherosclerosis remains ambiguous. The CRP classification by tertiles allowed to identify twice as many men at high risk than a normal categorization. Mortality due to cardiovascular diseases is higher for CRP levels between 3.0 and 9.9 mg/l than for CRP levels below 1.0 mg/l.[25] Similar results, independent of age, were observed in our subjects concerning widely recognized cardiovascular risk factors: decreased DHEA and HDL cholesterol levels, and cigarette smoking (TABLE 2).

TABLE 2 High-sensitivity C-reactive protein classification by tertiles, independent of age

	hs-CRP (mg/l)				*P*
	<1.0	1.0–3.0	3.0–9.9	>9.9	
number of patients	97	98	54	22	
serum DHEA (ng/ml)	12.95 (±6.15)	11.46 (±4.82)	11.27 (±5.52)	9.05 (±5.38)	<0.05
serum DHEA-S (μg/ml)	1.24 (±0.78)	0.98 (±0.77)	1.07 (±0.60)	1.19 (±0.97)	NS
serum LDL-cholesterol (mg/dl)	160.6 (±54.26)	162.31 (±44.54)	171.24 (±57.41)	151.32 (±41.77)	NS
serum HDL-cholesterol (mg/dl)	56.67 (±15.66)	52.38 (±14.48)	47.98 (±12.31)	42.32 (±8.75)	<0.0001
triglycerides (mg/dl)	138.38 (±122.23)	136.38 (±82.18)	160.37 (±90.33)	139.91 (±85.81)	NS
systolic blood pressure (mmHg)	140.82 (±22.43)	146.21 (±23.48)	151.67 (±25.83)	143.64 (±18.91)	NS
diastolic blood pressure (mmHg)	85.41 (±9.75)	86.21 (±10.73)	87.41 (±13.48)	85.68 (±10.38	NS
waist circumference (cm)	95.56 (±11.65)	99.71 (±10.02)	103.24 (±11.91)	104.36 (±16.86)	<0.0001
smoking (pack years)	308.09 (±357.21)	315.66 (±345.83)	455.83 (±480.68)	616.21 (±479.22)	<0.001

Abbreviations: HDL – high-density lipoprotein, LDL – low density lipoprotein, NS – nonsignificant, others – see TABLE 1

It is widely recognized that an elevated IL-6 level, as one of the main inflammatory markers, has a strong negative correlation with DHEA and, on the other hand, DHEA inhibits IL-6 secretion from macrophages, which supports evidence for a possible association between endocrine- and immunosenescence.[26]

Numerous sex hormones influence the level of inflammatory markers. In middle-aged and elderly men endogenous total and bioavailable estradiol levels are significantly associated with CRP.[27] In addition, DHEA-S levels have been shown to have a positive correlation with HDL levels and insulin sensitivity, and a negative one with CRP.[28]

HDL cholesterol plays the role of a positive predictor of the length of life. In our study, the HDL cholesterol concentration remained quite stable with age. We observed a negative correlation between HDL cholesterol and a positive one between TAG (r = 0.125, *P* <0.05) and serum CRP levels in aging men. These findings are consistent with previous studies.[29] No correlation with CRP levels was revealed for other evaluated lipid features.

The prevalence of MS in Poland is estimated at 17.7% for all men and 37% for men over 65 years of age.[30] A similar occurrence of MS (29.52%) was observed in our group.

In our study, there was a weak correlation between age and MS, more distinctly in middle-aged men (40–60 years). In addition, there was no correlation between adrenal androgens and the incidence of MS.[31] On the contrary, the rate of MS was evidently associated with inflammatory indices (except α_1-ACT) measured in our study.

In French population, out of different MS components in both sexes, waist circumference had the strongest positive correlation with CRP.[32] In our paper, anthropometric indices of MS (waist circumference >102 cm and BMI) showed positive correlations only with CRP. It is of note, however,

TABLE 3 Correlations between acute phase proteins and cigarette smoking, elevated blood pressure and anthropometrical as well as lipoid indices of metabolic syndrome

	HDL-cholesterol	Triglycerides	BMI	Waist circumference	Elevated blood pressure	Smoking
hs-CRP	–0.282 (*P* <0.0001)	0.125 (*P* <0.05)	0.197 (*P* <0.001)	0.258 (*P* <0.0001)	0.131 (*P* <0.05)	0.162 (*P* <0.001)
α_1-ACT	–0.126 (*P* <0.05)	NS	NS	NS	NS	0.141 (*P* <0.05)
transferrin	0.141 (*P* <0.05)	0.234 (*P* <0.0001)	NS	NS	0.123 (*P* <0.05)	–0.139 (*P* <0.05)

Abbreviations: BMI – body mass index, others – see TABLES 1 and 2

TABLE 4 The results of a multivariate logistic regression analysis of diseases associated with elevated high-sensitivity C-reactive protein levels

	Odds ratios	95% CI (lower–upper)
dementia	1.821	1.237–2.487
brain stroke in the past	1.784	1.136–2.394
metabolic syndrome (NCEP criteria)	1.673	1.183–2.274
ischemic heart disease	1.413	1.176–1.874
peripheral perfusion disturbances	1.378	1.082–1.791
osteopenia	1.314	1.027–1.744

Abbreviations: CI – confidence interval, NCEP – National Cholesterol Education Program

that sex plays an important role and modifies associations between indices of inflammation and anthropometric measurements, therefore the comparison showed a stronger association of CRP in women than in men, after adjusting for age and smoking.[33]

Our study showed positive correlations between cigarette smoking and increased CRP and α_1-ACT levels, which, on the other hand, are associated with a negative correlation with serum transferrin levels. This suggests that inflammation is one of the major factors promoting atherosclerosis and cardiovascular diseases among smokers, especially heavy smokers (Brinkmann Index, pack years >400).[34]

Smoking also induces protein production in the liver, including sex hormone-binding globulin. This may increase total serum androgen level, although not free androgen fraction. This probably explains the positive correlation between smoking and androgen levels, especially for total testosterone.

As for adrenal androgens, they are generally weakly bound to albumin. Even a slight elevation of total adrenal androgens in smokers may significantly impede evaluation of associations between DHEA/DHEA-S and other risk factors of atherosclerosis. In our study, there was no correlation between cigarette smoking and serum DHEA/DHEA-S levels (except for the group of 50-year-old patients, in which negative correlations were found: $r = -0.31$, $P < 0.02$).

It is possible that chronic inflammatory process represented by elevated IL-6, CRP and TNF levels in serum may be associated with a previous cancer diagnosis (especially lung, colorectal, and breast cancers).[35] However, we did not observe any correlations between the inflammatory markers and previously diagnosed malignant diseases.

Conclusions In conclusion, it may be stated that age is strongly correlated with acute phase proteins in men. DHEA (but not DHEA-S) serum levels are negatively correlated with CRP. Unlike adrenal androgens, CRP and transferrin (although not α_1-ACT) serum concentrations are associated with the occurrence of MS in men over 40 years of age.

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ARTYKUŁ ORYGINALNY

Ocena stężeń wybranych białek ostrej fazy oraz ich korelacje z androgenami nadnerczowymi i występowaniem zespołu metabolicznego w populacji mężczyzn powyżej 40 roku życia

Waldemar A. Herman[1], Aleksandra Seńko[2], Izabela Korczowska[3], Katarzyna Łącka[4]

1 Poradnia Endokrynologiczna „HERMED", Wschowa
2 Studenckie Towarzystwo Naukowe, Uniwersytet Medyczny im. K. Marcinkowskiego w Poznaniu, Poznań
3 Zakład Reumatologii i Immunologii Klinicznej, Uniwersytet Medyczny im. K. Marcinkowskiego w Poznaniu, Poznań
4 Katedra i Klinika Endokrynologii, Przemiany Materii i Chorób Wewnętrznych, Uniwersytet Medyczny im. K. Marcinkowskiego w Poznaniu, Poznań

SŁOWA KLUCZOWE

α_1-antychymotrypsyna, androgeny nadnerczowe, białko C-reaktywne, starzejący się mężczyźni, transferyna

STRESZCZENIE

WPROWADZENIE Mechanizmy zapalne oraz deficyt produkcji androgenów nadnerczowych biorą udział w patogenezie wielu schorzeń związanych ze starzeniem.

CELE Celem pracy była ocena stężeń wybranych ujemnych (transferyna) i dodatnich (α_1-antychymotrypsyna [α_1-ACT] i białko C-reaktywne [CRP]) białek ostrej fazy, a także zbadanie powiązań pomiędzy nimi a surowiczymi poziomami dehydroepiandrosteronu (DHEA) i jego siarczanu (DHEA-S), oraz antropometrycznymi i biochemicznymi wykładnikami zespołu metabolicznego u mężczyzn powyżej 40 roku życia.

PACJENCI I METODY U 271 losowo wybranych mężczyzn (mieszkańców województwa lubuskiego) w wieku 40–80 lat z powiatu lubuskiego oznaczono stężenie transferyny, α_1-ACT, CRP i stężenie androgenów nadnerczowych oraz oceniono antropometryczne i biochemiczne wykładniki zespołu metabolicznego (ZM).

WYNIKI Wiek jest silnie skorelowany z wykładnikami białek ostrej fazy u mężczyzn: pozytywnie z CRP i α_1-ACT (odpowiednio $r = 0{,}216$, $P < 0{,}001$ i $r = 0{,}193$, $P < 0{,}05$) oraz negatywnie z transferyną ($r = -0{,}268$, $P < 0{,}0001$). Stężenie CRP wykazuje ujemną korelację z DHEA ($r = -0{,}248$, $P < 0{,}05$), chociaż nie z DHEA-S. Nie wykazano również korelacji pomiędzy stężeniami α_1-ACT, transferyny oraz androgenów nadnerczowych. W przeciwieństwie do androgenów nadnerczowych, stężenia w surowicy CRP oraz transferyny (ale nie α_1-ACT) były związane z występowaniem ZM u mężczyzn w wieku >40 lat ($P < 0{,}001$).

WNIOSKI Zastosowanie testów prognostycznych oceniających systemowe wskaźniki uogólnionego stanu zapalnego (szczególnie CRP) może być pomocne (w przeciwieństwie do oceny stężeń DHEA oraz DHEA-S) w identyfikacji mężczyzn powyżej 40 roku życia cierpiących na zespół metaboliczny.

Adres do korespondencji:
lek. Waldemar A. Herman, Poradnia Endokrynologiczna „HERMED", ul. Zielona 8, 67-400 Wschowa, tel.: 065-540-34-27, fax: 065-540-34-27, e-mail: wherman@wschowa.com.pl
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