HIGH-SENSITIVITY C-REACTIVE PROTEIN (hsCRP) IN YOUNG ADULTS: RELATION TO AEROBIC CAPACITY, PHYSICAL ACTIVITY AND RISK FACTORS FOR CARDIOVASCULAR DISEASES

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ABSTRACT: Atheromatosis develops as a result of a chronic inflammatory process of the arteries. Inflammatory biomarkers, particularly high-sensitivity C-reactive protein (hsCRP), positively correlate with atheromatosis risk factors and can be used to estimate and predict the risk of cardiovascular events. The purpose of this study was to evaluate the relationship between hsCRP concentration and BMI, body composition, classical risk factors for cardiovascular diseases, energy expenditure for physical activity (WEE) and $\dot{V}O_2$max. 166 volunteers (78 women and 88 men) were included in the examinations. Their mean age was 20.2 ± 0.9 years. Health condition was described by the following variables: smoking, WEE, $\dot{V}O_2$max, body mass index (BMI), waist-to-hip ratio (WHR), fat mass (FM), fat-free mass (FFM), lipid profile, hsCRP, glucose and insulin concentration, and insulin resistance. Between the subgroups created on the basis of hsCRP concentration, in quartiles 1 to 3 and quartile 4, a comparative analysis was carried out. 79.5% of women and 69.3% of men had hsCRP values within the references ranges. Moderately high values were found in 14.1% of women and 22.7% of men and high in 6.4% and 7.9%, respectively. Mean values of BMI, FFM, WHR, WEE, $\dot{V}O_2$max, glucose and triglyceride concentration, and TC/HDL index were significantly lower, while FM and HDL were significantly higher, in women than in men. In the quartile 4 subgroup compared to the quartile 1-3 subgroup, we found significantly lower HDL concentration and a tendency for higher values of BMI (p=0.06) and TC (p=0.07) as well as higher percentages of smoking among men. In young, physically active, healthy persons, serum concentration of hsCRP is not related to physical activity or $\dot{V}O_2$max.

KEY WORDS: high-sensitivity C-reactive protein, risk factors, body composition, physical activity, aerobic capacity

INTRODUCTION

The inflammatory process plays an essential role in all phases of atherosclerosis development from initiation to clinical complications. This process begins in early childhood and can last throughout life, although its intensity changes depending on many factors which intensify or mitigate the inflammatory changes [6,19]. Limitation of the inflammatory process in the arteries is one of the most important strategies for primary prophylactic procedures as well as for secondary prevention against atheromatous complications, such as myocardial infarction and cerebral stroke [26,28].

C-reactive protein (CRP) is a non-specific indicator of the acute inflammatory state. It is used for detecting the inflammatory process in the course of acute injuries or infections. In the last decades, studies have pointed to a positive correlation between high sensitivity C-reactive protein (hsCRP) and intensity of the atheromatous process and the risk of cardiovascular events occurring as atheromatous complications [5,30,33]. Inflammatory markers, among them hsCRP,

seemed to be the most promising and proved useful in predicting the activities of inflammatory states and endothelial dysfunctions [7,15,25]. C-reactive protein as a mediator of cardiovascular disease can effect by decreases endothelial nitric oxide synthase, inducing a pro-atherogenic effect and the ability of plaque remodelling [4]. While hsCRP concentration below 1 mg$\cdot$l^{-1} is recognized as normal, the level between 1 mg$\cdot$l^{-1} and 3 mg$\cdot$l^{-1} is treated as moderately increased, which can indicate a slightly increased risk of cardiovascular events, whereas numerous researchers have recognized high values (hsCRP >3 mg$\cdot$l^{-1}) as an indicator increasing risk of cardiovascular (CV) events. Persons with diagnosed cardiovascular disease (CVD) as well as without clinical symptoms of CVD with hsCRP >3 mg$\cdot$l^{-1} have a higher risk of CV events than persons with hsCRP below this level [4,28,29]. Limitations for using CRP in identifying the occurrence and intensity of inflammatory processes arise from the non-specific character of this marker as the product of many metabolic and

inflammatory processes. Rich sources of inflammatory cytokines such as interleukins (IL-6, IL-1) and tumour necrosis factor (TNF-α) are abdominal fat cells. The main source of CRP is the liver. An increased level of IL-6 [15] is a strong stimulator for the secretion of CRP by the liver. Increased concentration of hsCRP strongly correlates with abdominal obesity, insulin resistance and, particularly, with the metabolic syndrome [12]. Physical activity has a favourable impact on traditional risk factors and decreases the risk of CVD. Systematic, moderate intensity physical activity may reduce the inflammatory process in the arteries as well decreasing the hsCRP level [2,13]. The beneficial effect of physical training on hsCRP concentration primarily concerns persons with overweight and obesity. However, numerous evaluations of the relationship between physical capacity changes and hsCRP have not confirmed the existence of such a relation [8].

The aim of this work was to evaluate the relationship between serum hsCRP concentration and factors determining health conditions, such as body mass index, body composition, traditional risk factors of cardiovascular diseases, physical activity and aerobic capacity.

MATERIALS AND METHODS

The research was conducted among 166 volunteers, students of the University of Physical Education in Warsaw (78 women and 88 men) of mean age 20.2 ± 0.9 years. The subjects were informed about the aim and methods of the examinations and were requested to abstain from smoking, drinking alcohol and exercising intensively 24 hours before examinations. The research was approved by the Senate Bioethical Committee of the University of Physical Education in Warsaw.

Physical activity was measured using the Seven-Day Physical Activity Recall (SDPAR) questionnaire and presented as weekly energy expenditure for sport and recreation activities. Body mass as well thigh and waist and hip circumferences were measured. Body mass index (BMI) and waist-to-hip ratio index (WHR) were calculated. Body compositions were assessed using the bioelectrical impedance method and BC 418 MA equipment (Tanita Co., Japan). Aerobic capacity expressed as maximal oxygen uptake ($\dot{V}O_2max$) was measured during a graded exercise test using a cycle ergometer (Ergomedic 874E, Monark, Sweden) and the expired air analyser Sensor Medics 2900/2900c (USA) [19] .

Blood was drawn after overnight fasting from the antecubital vein under aseptic conditions using disposable needles and syringes into plastic tubes containing lithium heparin. To separate plasma, blood samples were immediately centrifuged (15 min, 4000 rpm, 4° C) and stored at –70° C until analysis. Plasma glucose levels were determined using the oxidase method. Plasma triacylglycerols (TG), total cholesterol (TC), and HDL-cholesterol (HDL) concentrations were assayed colorimetrically. LDL-cholesterol (LDL) level was calculated based on Friedewald's formula. TC/HDL ratio was calculated. Analyses were performed using Randox commercial kits (Randox Laboratories, United Kingdom). In the serum, hsCRP was measured by immunochemiluminescence method using a Siemens Diagnostic set. Insulin concentrations were measured with the standard radioimmunoassay method with monoclonal antibodies against insulin, using BioSource commercial kits (Belgium). The insulin resistance index (HOMA-IR) was evaluated by the homeostasis assessment model and calculated from insulin and glucose concentrations {insulin ($\mu IU \cdot ml^{-1}$) x glucose ($mmol \cdot l^{-1}$) $\cdot 22.5^{-1}$} [32].

On the basis of individual distribution of hsCRP values, two subgroups of women and men were distinguished. The first subgroup included persons from quartiles 1-3 (of hsCRP values) (58 women and 66 men), whereas the second subgroup consisted of persons from quartile 4 (20 women and 21 men).

The Shapiro-Wilk test was used to determine whether hsCRP was normally distributed. To check differences of hsCRP concentration between genders, the Mann–Whitney U test was performed. Parametric data were analysed using two-way ANOVA with sex and hsCRP level as factors. Data are presented as mean ± SD. Statistical significance was set at $P < 0.05$. All calculations were done with SPSS version 17 (SPSS Inc., Chicago, IL).
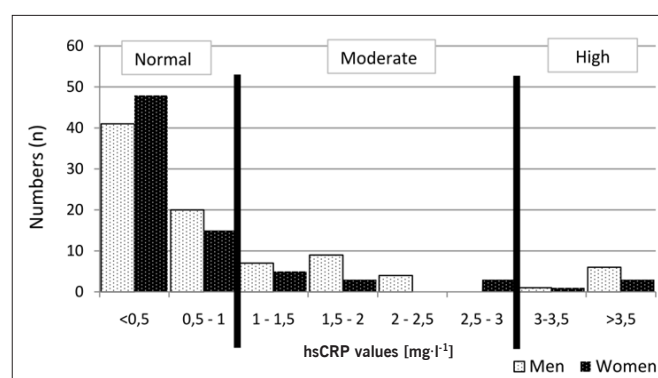

FIG. I. DISTRIBUTION OF hsCRP VALUES IN WOMEN AND MEN

TABLE I. NUMBER OF MEN AND WOMEN WITH NORMAL, MODERATE AND HIGH LEVEL OF hsCRP

	Women (n=78)			Men (n=88)			Statistical significance
	Normal (n=62)	Moderate (n=11)	High (n=5)	Normal (n=61)	Moderate (n=20)	High (n=7)	
hsCRP [$mg \cdot l^{-1}$]	0.42 ± 0.19	1.59 ± 0.58	6.48 ± 2.80	0.46 ± 0.20	1.70 ± 0.36	6.44 ± 4.10	n.a.
		0.98 ± 1.66			1.22 ± 1.97		p<0.05

Note: n.a. – not applicable
hsCRP reference range: normal <1.0 $mg \cdot l^{-1}$; moderate 1.0-3.0 $mg \cdot l^{-1}$; high >3.0 $mg \cdot l^{-1}$

TABLE 2. MEAN (± STANDARD DEVIATION) hsCRP IN SUBGROUPS 1-3 QUARTILES AND 4 QUARTILES, AMONG MEN AND WOMEN

| | Women (n=78) | | Men (n=87)[#] | | Statistical significance |
| | 1-3 quartiles | 4 quartile | 1-3 quartiles | 4 quartile | |
	hsCRP (n=58)	hsCRP(n=20)	hsCRP(n=66)	hsCRP(n=21)	
hsCRP [mg·l^{-1}]	0.39 ± 0.15	2.68 ± 2.64	0.52 ± 0.29	2.73 ± 1.62	n.a.
	0.98 ± 1.66		1.06 ± 1.26		p=0.73

Note: n.a. – not applicable, [#]one subject was excluded from further analysis due to high concentration of hsCRP, reflecting an active infectious or inflammatory process

RESULTS

A frequency histogram of hsCRP concentrations in the studied population is shown in figure 1; the distribution is highly skewed. Sixty-three women (79.5%) and 61 men (69.3%) had their hsCRP concentration within reference limits, 8 (14.1%) and 16 (22.7%) respectively had moderately increased values, while 3 (6.4%) women men and 6 (7.9%) men had high values. The mean hsCRP concentration among men and women, classified in reference ranges, is presented in Table 1. One man of significantly increased hsCRP (15.3 mg·l^{-1}), reflecting an active infectious or inflammatory process, was excluded from the observation and subsequent analysis.

Due to the small number of subjects in the subgroup with high hsCRP values, the comparative analysis was conducted between the subgroup composed of quartiles 1 to 3 and quartile 4. Mean values of hsCRP in the subgroups comprising quartiles 1-3 and quartile 4, among men and women, are summarized in Table 2. The mean values of hsCRP in women and men in quartiles 1-3 stayed within the normal range while in quartile 4 they were 2.68 ± 2.64 mg·l^{-1} in women and 2.73 ± 1.62 mg·l^{-1} in men. The mean concentration of hsCRP did not differ between men and women.

In order to determine the relationship between body composition and analysed parameters of physical condition and energy expenditure for physical activity in comparative hsCRP subgroups, a two-way ANOVA was performed and the results shown in Table 3. The ANOVA found a significant main effect (of sex only) for BMI, body composition, WHR, WEE and V̇O$_2$max, but no interaction effects with sex and hsCRP level.

TABLE 3. BODY COMPOSITION, PHYSICAL ACTIVITY AND AEROBIC CAPACITY IN hsCRP SUBGROUPS AMONG MEN AND WOMEN

| Variables | Women | | Men | | Statistical significance | |
	1-3 quartiles hsCRP (n=58)	4 quartile hsCRP (n=20)	1-3 quartiles hsCRP (n=66)	4 quartile hsCRP (n=21)	Sex	hsCRP level
BMI	21.12±2.02	21.93±2.95	23.29±2.22	24.09±3.14	p<0.001	p=0.06
FM [%]	22.90±5.03	23.06±4.62	12.21±3.93	13.87±5.65	p<0.001	p=0.28
FFM [%]	77.10±5.03	76.94±4.62	87.79±3.92	86.13±5.65	p<0.001	p=0.28
WHR	0.84±0.06	0.85±0.06	0.89±0.06	0.92±0.05	p<0.001	p=0.20
WEE [kcal·wk^{-1}]	3542 ±2241	3474±2542	5394±2485	5277±2439	p<0.001	p=0.83
V̇O$_2$max [ml·kg^{-1}·min^{-1}]	40.68±4.60	41.63±4.65	47.72±5.97	49.84±6.85	p<0.001	p=0.49
Smoking [%]	10.3%	10%	1.5%	14%	p=0.18	-

Note: BMI - body mass index, FM - fat mass, FFM - fat free mass, WHR - whist to hip ratio index, WEE - weekly energy expenditure for sport and recreation physical activity

TABLE 4. BIOCHEMICAL RISK FACTORS OF ATHEROMATOSIS IN hsCRP SUBGROUPS AMONG MEN AND WOMEN

| Variables | Women | | Men | | Statistical significance | |
	1-3 quartiles hsCRP (n=58)	4 quartile hsCRP (n=20)	1-3 quartiles hsCRP (n=66)	4 quartile hsCRP (n=21)	Sex	hsCRP level
TG [mmol·l^{-1}]	0.65±0.28	0.73±0.36	0.83±0.38	0.77±0.36	p=0.06	p=0.88
TC [mmol·l^{-1}]	4.63±0.57	4.37±0.40	4.56±0.73	4.39±0.75	p=0.85	p=0.07
HDL [mmol·l^{-1}]	1.60±0.31	1.46±0.21	1.45±0.35	1.35±0.40	p<0.05	p<0.05
LDL [mmol·l^{-1}]	2.73±0.52	2.57±0.46	2.71±0.79	2.54±0.70	p=0.84	p=0.16
TC/HDL	2.98±0.62	3.04±0.45	3.31±0.95	3.47±1.04	p<0.01	p=0.46
Glucose [mmol·l^{-1}]	4.47±0.45	4.42±0.28	4.78±0.58	4.76±0.49	p<0.001	p=0.68
Insulin [mmol·l^{-1}]	8.77±2.94	7.91±3.03	7.20±2.95	6.84±1.77	p<0.01	p=0.22
HOMA-IR	1.74±0.58	1.54±0.59	1.57±0.81	1.43±0.43	p=0.26	p=0.17

Note: TG - triglycerides, TC - total cholesterol, HDL - high density cholesterol, LDL - low density cholesterol, TC/HDL - atheromatosis index, HOMA-IR - an index of insulin resistance

Results of testing parameters of biochemical risk factors of atheromatosis in comparative hsCRP subgroups are summarized in Table 4. The ANOVA found significant main effects (sex and hsCRP) for HDL, and a significant main effect of sex for TC/HDL, glucose and insulin. There was no interaction effect of sex and hsCRP level for any parameter.

DISCUSSION

The role of traditional risk factors in pathogenesis and development of cardiovascular disease is commonly acknowledged while the applicability of inflammatory state biomarkers in estimating the risk of cardiovascular incidents remains controversial [28,36].

Numerous studies of the last decade have proved that hsCRP when combined with the traditional CVD risk factors can be used as a biomarker which correlates with dyslipidaemia, type 2 diabetes or obesity, all being traditional risk factors, as well as the level of physical activity and cardiorespiratory fitness.

According to Ridker, adding hsCRP to traditional risk allows for reclassification of about 30% of moderate-risk patients to either the high- or low-risk category [30].

Many studies indicate a strong positive correlation between hsCRP and fatness or BMI [14]. A relation is also emphasized between increased hsCRP values and insulin resistance and type 2 diabetes [35]. Also a relationship was established between regular physical activity and a low level of hsCRP. These data, however, have not been confirmed in other recent research [24,36].

Koenig and co-workers found a strong positive correlation of CRP and age, BMI, smoking and diabetes. Individuals who smoked had their CRP concentration increased two to three times when compared to non-smokers. Obese persons of BMI >30 have been found to have CRP concentration twice as high as persons with BMI <25 [17].

In the Jupiter studies [9], statin treatment was applied according to the criterion of high hsCRP alone, without high cholesterol concentration (hsCRP >2 mg/dl and LDL <130 mg/dl). As a result, a hsCRP concentration reduction by 37% was achieved as well as reduction of the cardiovascular fatality rate by 47% and total fatality by 20%. Statin treatment also lowered the LDL concentration by 50%. According to the authors, the JUPITER studies confirmed the relationship between the likelihood of cardiovascular events and hsCRP and LDL levels achieved after the statin treatment.

It was also proved that changes in the life style leading to improvement of physical fitness and reduction of adipose tissue/body fat may lower hsCRP and reduce the risk of cardiovascular events [16,22]. Research [3,10,11] also shows an inverse relationship between physical activity, cardiovascular fitness and hsCRP concentration.

Other authors, however, did not find relationships between physical activity level and hsCRP [27]. Similarly, Kelly and co-workers stated [14] that positive changes in BMI, body fat and $\dot{V}O_2$max achieved through aerobic exercise were not followed by significant lowering of hsCRP. The authors suggested that intense physical activity probably does not considerably affect low (<1 mg·l^{-1}) and moderately increased (1.0-3.0 mg·l^{-1}) hsCRP values. However, it is not clear whether it affects the reduction of high (>3.0 mg·l^{-1}) hsCRP values. Also, some current review studies emphasize that hsCRP is a weak predictor of coronary heart disease compared with other markers and clinical information [1].

The present study included young healthy persons of relatively high physical activity and average or high aerobic fitness. While analysing the level of traditional risk factors in the previous study, normal mean values of body composition and biochemical indices have been found in this group; moreover, only 9% of female subjects and 5% of males smoked cigarettes [20].

Significant differences have been found among the indices analysed depending on the sex of the subjects. The mean values of BMI, FFM, WHR, energy expenditure in recreational as well as sports physical activity, $\dot{V}O_2$max, systolic and diastolic blood pressure, glucose concentration, triglycerides (TG) and the TC/HDL index were lower, while FM (%), while HDL was significantly higher in women than in men.

As only 12 subjects (7 men and 5 women) had high hsCRP values, two comparative subgroups were created on the basis of the hsCRP value, namely, quartiles 1-3 and quartile 4. The mean hsCRP concentration values in those groups did not differ significantly with respect to sex, showing a tendency for lower values in women. The only significant differences to be found between subgroups from quartiles 1-3 and quartile 4 were those of HDL cholesterol concentration, which was higher in the quartile 1-3 subgroup. Quartile 4 tended to have higher values of BMI (p=0.06) and TC (p=0.07) than the group of lower quartiles. Among men from quartile 4 there was also a higher percentage of smokers (14% vs. 1.5%). The lack of a strong relationship of selected traditional risk factors (biochemical and somatic) with hsCRP revealed in this study confirm a need for further investigations in this area.

No relationship was found between hsCRP concentration and the physical activity or aerobic capacity as expressed by $\dot{V}O_2$max. These findings are in contrast with selected randomized clinical trials. Kuo H.-K. et al. [18] found that in adults CRP concentration levels are inversely related to cardiorespiratory fitness and could be an important indicator of exercise tolerance, and they suggested that cardiorespiratory fitness may be one of the mechanistic factors in the pathway from chronic inflammation to functional disabilities or CVD. McVean J.J. et al. [21] demonstrated a negative correlation between CRP concentration and maximum oxygen consumption in non-obese children. On the other hand, there are other studies showing no association of hsCRP concentration and maximal oxygen uptake, even in overweight women [23]. Kelly G.A. et al. [14], in a meta-analysis of randomized controlled trials, suggested that aerobic exercise does not reduce CRP concentration in adults, but does improve measures of body composition and physical fitness, which are known as important factors in CVD prevention. In a recent study, Siahkouhian M. and Esmaeilzadeh S. [31] reported lack of an association between hsCRP

and maximal oxygen consumption both in athletes and non-athletes. In our opinion, it is still no clear that improvements in aerobic fitness reduce CRP, or whether an effect is mediated entirely by a reduction in body fat. The findings of previous studies in this area are mixed.

Although in the present study no relationship between aerobic capacity and concentration of hsCRP was found, it is recommended to avoid depreciating the role of physical exercise in the population with high risk of CVD because it is proved that physical activity reduces the severity of CVD risk factors and risk of all-cause mortality. It is believed that the greatest benefits are obtained by inactive persons who become moderately active, but even at high levels of activity benefits accrue from additional activity [34].

The results of research from recent years show that reclassification of risk of cardiovascular disease after the application of CRP is moderate or unstable. Adding CRP to the evaluation of cardiovascular risk gives little improvement to foreseeing cardiovascular events, nor does it improve prognosis. The differences in the risk prediction of incidents of cardiovascular disease on the basis of CRP>3 mg$\cdot$l^{-1} vs. <1 mg$\cdot$l^{-1} have not been proved satisfactorily [15, 27].

Similarly, the Copenhagen City Heart Study [36], including numerous persons from the general population and several years of observation, demonstrated that increased CRP concentration is associated with higher all-cause mortality. Increased CRP does not seem to be a causal factor of early cardiovascular deaths, but it is more probable that it indicates a hidden inflammatory process which leads to early deaths through intensification of thrombosis and atheromatosis.

CONCLUSIONS

Mean values of hsCRP in women were significantly lower than in men. High values of hsCRP were found in 6.4% of women and 7.9% of men. In the quartile 4 subgroup, as compared with the subgroup of quartiles 1-3, lower HDL values were found as well as a higher percentage of smokers and a tendency for higher BMI values (p=0.06) and TC (p=0.07). No relationship was found between hsCRP and physical activity and the $\dot{V}O_2$max value in young, physically active, healthy persons of average or high aerobic fitness.

Conducting a study on a larger group of people, including those of sedentary type as well as increased exposure to risk factors, would allow for a critical analysis of the results obtained so far.

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