



The relationship between adiposity parameters and C-reactive protein values in overweight and obese women

Odnos između parametara gojaznosti i vrednosti C-reaktivnog proteina kod predgojaznih i gojaznih žena

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Abstract

Background/Aim. Overweight/obesity has become important health problem in developed countries. It may be related to a presence of low-grade inflammation in white adipose tissue. The aim of this study was to investigate the levels of inflammatory marker C-reactive protein (CRP) and its relation to anthropometric parameters in overweight and obese females. **Methods.** This study included 200 apparently healthy, overweight and obese women (18–45 years). Their standard and alternative anthropometric parameters [body mass index (BMI), percentage of fat (%F), waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), body adiposity index (BAI)] were determined and correlated to serum CRP concentration. **Results.** Average CRP level was 5.56 ± 2.43 mg/L, and it significantly positively correlated to all investigated anthropometric parameters. There was significant difference between overweight and obese group in all investigated anthropometric parameters, as well as in CRP values. When investigated separately, according

to BMI, values regarding obese females showed significant correlation between CRP and every investigated anthropometric parameter. In overweight subjects, no such correlation was recorded. In the obese group, all investigated parameters were significantly related to F. In overweight subjects, body weight (BW), BMI, WC and WHtR showed significant relation to F. **Conclusion.** The significant difference between the overweight and obese group in all parameters of central obesity was found as well as in the CRP levels. In the obese group, we found strong correlation between adiposity measured by fat percentage and parameters of central obesity, while in the overweight group WHR and BAI did not correlate to fat percentage. Our results confirmed that CRP is a valuable marker of metabolic risk in obese females, and BMI, although not so new, is still reliable parameter of adiposity.

Key words: obesity; overweight; women; anthropometry; c-reactive protein.

Apstrakt

Uvod/Cilj. Prekomerna telesna masa i gojaznost postali su značajan zdravstveni problem u razvijenim zemljama, a mogu biti povezani sa prisustvom hronične inflamacije niskog intenziteta u belom masnom tkivu. Cilj rada bio je da se ispituju nivoi markera inflamacije, C-reaktivnog proteina (CRP), i njegova povezanost sa standardnim antropometrijskim parametrima kod predgojaznih i gojaznih žena. **Metode.** Studijom je bilo obuhvaćeno 200 zdravih žena (18–45 god) kojima su određeni standardni i alternativni antropometrijski parametri [indeks telesne mase (BMI), procenat masti (%F), obim struka (WC), odnos obima struka i kukova (WHR), odnos obima struka i visine (WHtR), kao i indeks telesne masnoće (BAI)] koji su zatim korelisani sa koncentracijama

CRP u serumu. **Rezultati.** Prosečna vrednost nivoa CRP u serumu u celoj grupi iznosila je $5,56 \pm 2,43$ mg/L i utvrđena je njegova značajna pozitivna korelacija sa svim ispitivanim antropometrijskim parametrima. Uočena je statistički značajna razlika između grupa predgojaznih i gojaznih žena u svim ispitivanim antropometrijskim parametrima, kao i u pogledu koncentracije CRP. U grupi gojaznih ispitanica utvrđena je značajna povezanost između CRP i svih antropometrijskih parametara, dok u predgojaznoj grupi nije zabeležena statistička značajnost. U grupi gojaznih, svi antropometrijski pokazatelji pokazali su značajnu korelaciju sa procentom telesne masti, a kod predgojaznih žena, korelacija je bila značajna samo za telesnu masu, BMI, WC i WHtR. **Zaključak.** Između predgojaznih i gojaznih ispitanica postoji značajna razlika u pogledu svih pokazatelja centralne gojaznosti, kao i u pogledu

koncentracije CRP u serumu. U grupi gojaznih, pokazana je značajna korelacija između sadržaja masti, izraženog kao procenat masnoće, i svih pokazatelja visceralne distribucije masti, dok u grupi predgojaznih značajna povezanost nije urađena za WHR и BAI. Naši rezultati potvrđuju da CRP može predstavljati značajan marker metaboličkog rizika kod

gojaznih žena, kao i da je BMI, iako spada u tradicionalne parametre, i dalje pouzdan pokazatelj sadržaja telesne masti.

Ključne reči:
gojaznost; telesna masa, prekomerna; žene; antropometrija; c-reaktivni protein.

Introduction

Overweight/obesity has become important health problem in developed countries. It may be related to presence of low-grade inflammation in white adipose tissue¹. Precise mechanisms of chronic inflammation induction in obesity as well as the relation between obesity and inflammatory markers are yet to be explained^{1,2}. So far, the importance of C-reactive protein (CRP), as the most versatile inflammatory marker, is still in the spotlight.

CRP is acute-phase protein and inflammatory marker. Increased concentrations of CRP are present in serum after tissue injury, infection and inflammation³. Its synthesis takes place in liver, and is mostly regulated by interleukin-6 (IL-6). Numerous surveys classified CRP as important marker of inflammation, which may indicate early vascular lesions, and may be a predictor of cardiovascular events, even in apparently healthy population⁴. Most of the studies confirm that even levels below the accepted upper physiological limits (1 mg/dL) may indicate the increased risk of heart and cerebral stroke, peripheral atherosclerosis, and sudden death in both gender^{1,5,6}. CRP outstands as independent risk factor, apparent from traditional risk factors such as increased total cholesterol, increased levels of glucose and homocystein, hypertension, age, high body mass index (BMI), smoking and physical inactivity⁷.

In general, recent studies indicate that white adipose tissue produces numerous mediators, for example, cytokines tumor necrosis factor alpha (TNF α) and IL-6. In addition, in obese persons, white adipose tissue is infiltrated by macrophages with increased local production of proinflammatory mediators. These factors promote acute phase reaction and chronic inflammation in obese persons⁴.

However, some authors proposed the existence of a subgroup of obese persons who are metabolically normal (without increased risks of heart diseases, type 2 diabetes, hypertension, stroke, gallbladder disease, cancers, etc.)⁸. They hypothesize that in this subpopulation obesity seems to be uncomplicated and is characterized by early onset, hyperplasticity of otherwise normal adipocytes, and peripheral type of fat distribution. The inflammation in these persons should be absent, and they supposed to have normal levels of inflammatory markers.

The aim of this study was to investigate the levels of inflammatory marker CRP and its relation to standard anthropometric parameters [body mass (BM), BMI, percentage of fat (F), waist circumference (WC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR)], as well as to alternative parameter, the body adiposity index (BAI), in population of apparently healthy overweight and obese females.

Methods

This study enrolled 103 overweight (BMI between 25 and 29.9 kg/m²) and 97 obese (BMI \geq 30 kg/m²) females, nonsmokers, aged 18–45 years, without any comorbidities, and with regular menstrual cycles. Our study did not include persons with: clinically confirmed hypertension, glucose intolerance or diabetes, other endocrine or systemic inflammatory diseases, cardiovascular and/or cerebrovascular diseases, malignant diseases, pregnancy, and those with CRP values higher than 10 mg/L at the moment of investigation. None of them had previous history of stroke, transitory ischemic attack, angina pectoris, heart stroke, or congenital heart abnormality. At the moment of investigation, they did not take any medical drugs, supplements, oral contraceptives, or hormonal substitution drugs. Investigation was approved by the local Ethical Committee and was conducted in Department of Nutrition, Institute of Hygiene, Military Medical Academy, Belgrade, Serbia, during 2013 and 2014.

Standard anthropometric measurements were performed: body weight (BW), body height, WC and hip circumference⁹, skinfold thickness, and followed parameters were calculated: BMI [kg/m²], percentage of fat (%F)¹⁰, waist-to-hip ratio (WHR), waist-to-height ratio (WHtR)⁹, and BAI [hip circumference (cm)/height^{1.5} (m) – 18]¹¹. High sensitive CRP was measured in serum using enzymatic kits (Roche Diagnostics, Basel, Switzerland) on a Siemens autoanalyser (Dimension[®], RxL Max, Siemens Dade Behring). Concentrations lower than 1 mg/L refer to low risk for cardiovascular diseases, values between 1 and 3 mg/L were in an average range, and values higher than 3 mg/L were considered as high risk⁶. WC less than 80 cm considered normal, between 80 and 87.9 cm referred to increased risk of metabolic complications, and \geq 88 cm referred to substantially increased risk⁹; WHR \geq 0.8 was also considered increased, as well as WHtR \geq 0.62¹².

Obtained data were statistically processed and presented as means \pm SD; some of the data were presented as proportions (%). Difference between groups and correlation between chosen parameters and CRP values were analyzed by Student's *t*-test (χ^2 test for categories) and Spearman's rank correlation (*r*), respectively. Statistical significance was accepted at $p < 0.05$.

Results

Anthropometric parameters and serum concentrations of CRP in all 200 investigated subjects together are presented in Table 1.

Average CRP was 5.56 ± 2.43 mg/L, and significantly positively correlated to all investigated anthropometric parameters (BW: $r = 0.3329$, $p < 0.01$; BMI: 0.3567 , $p < 0.01$;

Table 1
Anthropometric parameters and C-reactive protein (CRP) values of the study subjects

Parameters	$\bar{x} \pm SD$	min-max
Age (year)	31.12 \pm 7.26	18-45
BW (kg)	87.99 \pm 14.99	60.60-144.00
BMI (kg/m ²)	31.16 \pm 5.08	25.04-51.24
%F	41.04 \pm 4.98	28.70-56.00
WC (cm)	95.75 \pm 12.98	70.00-148.00
WHR	0.85 \pm 0.08	0.65-1.12
WHtR	0.57 \pm 0.08	0.43-0.87
BAI	33.93 \pm 4.99	23.06-50.40
CRP (mg/L)	5.56 \pm 2.42	0.82-10.00

BW – body weight; **BMI** – body mass index; **%F** – fat percentage; **WC** – waist circumference; **WHR** – waist-to-hip ratio; **WHtR** – waist-to-height ratio; **BAI** – body adiposity index; **CRP** – C-reactive protein.
 \bar{x} – mean value; **SD** – standard deviation.

%F: 0.2589, $p < 0.01$; WC: 0.3645, $p < 0.01$; WHR: 0.2417, $p < 0.01$; WHtR: 0.3637, $p < 0.01$, and BAI: 0.2063, $p < 0.05$).

Statistical analysis showed the significant difference between the overweight and obese group for all investigated anthropometric parameters, except for the age as well as CRP values (Table 2).

Moreover, when the overweight and obese groups were presented separately, according to BMI, the different correlation between anthropometric parameters and CRP values were found. The results are presented in Table 3.

In both groups, there was no statistically significant cor-

relation between CRP levels and age. In addition, in overweight subjects, no significant correlation was recorded between CRP and any anthropometric measurement or index whatsoever. On the other hand, in the obese group, every investigated anthropometric parameter was significantly correlated to CRP levels.

Percentage of fat measures body adiposity. In both groups, age was not significantly correlated to this parameter. In the overweight subjects, neither WHR nor BAI showed significant relation to %F, opposite to BW, BMI, WC and WHtR. In the obese group, all investigated parameters were significantly related to %F.

Table 2
Anthropometric parameters and C-reactive protein (CRP) values in overweight and obese groups of women

Parameter	Overweight	Obese	<i>p</i>
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	
Age (years)	31.55 \pm 7.66	30.69 \pm 7.60	n.s.
BW (kg)	77.82 \pm 6.89	98.80 \pm 13.67	< 0.000
BMI (kg/m ²)	27.49 \pm 1.35	35.05 \pm 4.67	< 0.000
%F	38.23 \pm 3.26	44.03 \pm 4.75	< 0.000
WC (cm)	88.13 \pm 6.94	103.84 \pm 13.03	< 0.000
WHR	0.83 \pm 0.07	0.87 \pm 0.08	0.0011
WHtR	0.52 \pm 0.04	0.62 \pm 0.08	< 0.000
BAI	30.86 \pm 2.55	37.19 \pm 4.89	< 0.000
CRP (mg/L)	4.95 \pm 2.29	6.21 \pm 2.41	0.0002

For abbreviations see under Table 1.

Table 3

Spearman's correlation coefficient (r) in overweight and obese women

Parameter	Correlation to CRP, (r; <i>p</i>)		Correlation to %F; (r; <i>p</i>)	
	overweight	obese	overweight	obese
Age	-0.1225; n.s.	-0.0525; n.s.	-0.1152; n.s.	0.0843; n.s.
BW	0.0625; n.s.	0.3101; < 0.01	0.2000; < 0.05	0.6077; < 0.01
BMI	0.1927; n.s.	0.3103; < 0.01	0.4664; < 0.01	0.6179; < 0.01
WC	0.1206; n.s.	0.3628; < 0.001	0.3679; < 0.01	0.6366; < 0.01
WHR	0.0935; n.s.	0.2831; < 0.001	0.1693; n.s.	0.4566; < 0.01
WHtR	0.1493; n.s.	0.3455; < 0.001	0.4081; < 0.01	0.6096; < 0.01
BAI	0.0749; n.s.	0.2806; < 0.01	0.0749; n.s.	0.3776; < 0.01
F	-0.064; n.s.	0.2757; < 0.001		
CRP			-0.064; n.s.	0.2757; < 0.001

n.s. – non significant.

For abbreviations see under Table 1.

According to BMI, all subjects were overweight or obese. However, fat distribution was different: in the overweight group, 10 (9.7%) women had normal values of WC, in 52 (50.5%) women the recorded values were in the range of increased risk of metabolic complications and in 41 (39.8%) women substantially increased risk values were recorded. In the obese group, there was only 1 person with normal WC, 5 with values suggesting increased risk, and 91 (93.8%) with substantially increased risk. These differences were statistically significant ($p < 0.05$). When risk is estimated according to WHR, there were 37 (35.9%) subjects in the overweight group with normal WHR, and 66 (64.1%) with increased WHR. In the obese group, normal WHR was recorded in 17 (17.5%) subjects and increased WHR in 80 (82.5%). In the overweight group, all subjects had normal WHtR, while in the obese group 33 (34%) of them had increased risk, i.e. $WHtR \geq 0.62$ ($p < 0.05$).

In addition, 2 persons in the overweight group had CRP concentration in the range of low risk, 15 persons in the range of average, and 86 (83.5%) in the range of high risk of cardiovascular disease development. In the obese group, increased values of CRP were recorded in 93 (95.9%) subjects, with 4 persons in average range and no subject in low risk range, but these differences were not statistically significant.

Discussion

Obesity is extensively spread disease, which is, due to its metabolic effects, considered the most frequent risk factor for development of diabetes, hypertension and atherosclerosis. However, obesity itself, when defined according to body mass, is less powerful predictor comparing to central obesity, so recently anthropometric parameters have been adopted in order to achieve better discrimination of body adiposity and metabolic risk. The accuracy and usefulness of numerous parameters were analyzed, such as WC, WHR, WHtR¹², and BAI¹¹.

The important difference between men and women regarding body fat storage is considering the fact that women have more adipocytes at the start of their adult life (hyperplastic obesity), so they may accumulate more fat compared to men¹³. Later, process of fat accumulation is particularly rapid in subcutaneous abdominal area as the result of adipocyte hypertrophy. These observations served as foundations for suggestions that, especially in young women, obesity without comorbidities might be present. In our study, all women were apparently healthy and relatively young (18–45 years). However, the average levels of CRP were elevated in both groups, particularly in the obese one, and the difference between groups was statistically significant.

Despite the absence of metabolic diseases, according to our results, average WC of all investigated subjects was 95.55 ± 12.98 cm, and WHR 0.85 ± 0.08 , suggesting high frequency of visceral obesity, and increased risk of metabolic complications. However, when observed as WHtR ratio, visceral obesity was less pronounced: mean value was 0.57 ± 0.08 , which is below the accepted limit of increased risk (0.62). In the overweight group, we found 90% of women with increased or substantially increased values of

WC, but all subjects in this group were in the normal range of WHtR. In the obese group, we found that almost every woman had increased WC, but only one-third was in the range of increased metabolic risk when categorized according to WHtR. WC was significantly related to increased risk of hypertension even in young (22–30 years) student population in Serbia¹⁴.

To date, the investigations were directed to obese or morbid obese men and women. Studies performed on overweight persons are sparse. Considering the frequency of overweight persons in our population, and the possibility of prediction the cardiovascular risk regardless of age and actual health status, we wanted to investigate this problem in particular.

The major characteristic of our results is significant difference observed between overweight and obese subjects in almost all important features. Besides the anthropometric differences which were expected (BW, BMI, %F), in the overweight group we recorded significantly lower values of parameters that reflect the metabolic risk: WC, WHR, WHtR, as well as significantly lower values of inflammatory marker CRP. CRP is a strong predictor of future vascular events, and the value obtained from initial blood sample may be useful in prediction even after twenty years⁶. When analyzed several large studies conducted both in Europe and the USA, the same author found the strong relationship between CRP concentrations and future cardiovascular events, apart from other risk factors. Prospective random study from MONICA project has processed large sample of initially health middle aged population and indicated the same strong relationship⁵. Moreover, the results from this study demonstrated that obese persons showed two-fold higher concentrations of CRP compared to persons with normal BMI. The importance of central obesity is confirmed in numerous studies, which proved stronger correlation of WC and WHR to higher cardiovascular risk, compared to BMI¹⁴. The role of visceral obesity is particularly important in persons with normal BMI.

The results from the Women's Health Study which enrolled 39,876 middle-aged women showed that women with CRP levels higher than 75th percentile (> 0.59 mg/dL) also had higher BMI, WC and WHR. After adjusting for age, CRP demonstrated strong correlation with BMI and W, but less strong correlation with WHR¹⁵. The results of our investigation confirmed the strong correlation between CRP levels and parameters of central adiposity in obese women, but also with BMI. This association is absent in overweight females.

A meta-analysis of 10 studies with a total of 88,514 subjects concluded that discriminatory power of markers of central obesity, such as WHtR, regarding cardiovascular risk is better than BMI, but this difference is small, insignificant, and with no clinical relevance¹². Our results confirmed that WHtR significantly correlated with overall fat percentage, both in the overweight and obese group, but the correlation between WHtR and CRP was present only in the obese group.

The same pattern is observed for BAI. In this study we also estimated BAI as a new parameter of body adiposity,

which is very simple for use, since it does not require weight measurement. It is calculated from body height and hip circumference¹¹ and can be used to reflect overall fat (visceral and subcutaneous) percentage in both sexes and in different ethnicity. Although in mentioned large study conducted by Bergman et al.¹¹, BAI was defined as a strong predictor of fat percentage, our result showed significant correlation between these two parameters only in obese women, and not in overweight ones. In general, in the obese group we found that all anthropometric parameters and indices (BW, BMI, WC, WHR, WHtR and BAI) were significantly correlated to %F and hence reflect the overall adiposity.

Central obesity is strongly related to metabolic risk and has been identified as a useful predictor of metabolic syndrome. The link that connects visceral obesity to its metabolic complications may be systemic insulin resistance, however, the influence of adipose tissue on insulin sensitivity is not clear enough. Chronic inflammation is common characteristic of metabolic syndrome, particularly related to insulin resistance. On the other hand, infection and inflammation are also related to insulin resistance, while visceral obesity is related to chronic low-grade inflammation. Hence, these observations may introduce inflammation as a possible mechanism of effects of obesity on insulin resistance.

The proposed mechanism of induction of inflammation in obesity is increased secretory activity in adipose tissue. Adipose tissue is the site of production of numerous secretory factors (adipokines), with pro- and anti-inflammatory effects¹⁶⁻¹⁸. Homeostasis is maintained due to the balance in secretion of different factors. This homeostasis may be impaired in presence of adipose tissue enlargement, resulting in dysregulation of adipokine production, and following local and/or systemic inflammatory reaction¹⁹. Excessive fat tissue produces proinflammatory factors, particularly TNF α and IL-6, but also generates acute-phase reactants such as plasminogen activator inhibitor-1 (PAI-1), haptoglobin, serum amyloid A, which are the major contributors of low-grade systemic inflammation²⁰. Obese persons seem to have increased activation of kinases in adipose tissue, and subsequently increased expression of inflammatory cytokines²¹. Levels of inflammatory cytokines in obese men and women are higher than in non-obese ones, and might be related to insulin resistance²². TNF α and other pro-

inflammatory cytokines can contribute to inhibition of insulin receptor substrate-1 by inducing serine phosphorylation. Enlarged adipose tissue in humans also leads to infiltration of inflammatory immune cells and macrophages with substantial loss of functional programming, which may promote inflammation^{23,24}.

These inflammatory mediators then induce synthesis of acute-phase reactants in liver, among them CRP, which is induced largely by IL-6. This results in increased serum concentration of these molecules even in healthy obese persons²⁵, including children²⁶. These observations are in agreement with our results.

In order to explore this suggested association, Pannaciuoli et al.³ investigated CRP levels in apparently healthy women of different age (18–60 years), and with different nutritional status (normal weight, overweight, and obese) in relation to body composition and fat distribution. They found that CRP concentrations are correlated to fat mass, regardless of age, but visceral adiposity (measured by WC) was stronger predictor of CRP compared to overall fat mass. In addition, another study performed in 119 young (20–40 years) and healthy obese adults of both sexes showed that fat mass and fat percentage were predictors of CRP levels in a group of females under 30 years, but body composition did not predict CRP neither in older females, nor in males of any age²⁷.

Conclusion

In population of apparently healthy relatively young women, we found significant difference between the overweight and obese group in all parameters of central obesity, as well as in CRP levels. However, we recorded elevated concentrations of CRP even in overweight women. CRP levels were positively correlated to BMI, WC, WHR, WHtR, BAI and in the obese group, regardless of age, but in the overweight group no correlation was recorded. Finally, in the obese group, we found strong correlation between adiposity measured by fat percentage and parameters of central obesity, while in the overweight group WHR and BAI did not correlate to fat percentage. Our results confirmed that CRP is a valuable marker of metabolic risk in obese females, and BMI, although not so new, is still a reliable parameter of adiposity.

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