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Original article

Anthropometric and metabolic parameters in relation to high sensitivity C-reactive protein in Montenegrin population with type 2 diabetes

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Summary. *Background/Aim:* High sensitivity C-reactive protein (hsCRP) in widely recognized inflammation marker associated with increased cardiovascular disease (CVD) risk. Since CVD is a common complication in type 2 diabetes (DM2), and since there is a high prevalence of obesity and DM2 in Montenegro, we aimed to examine the association of hsCRP with anthropometric and metabolic parameters in the cohort of individuals with DM2. Additionally, we aimed to examine the gender difference in CVD risk as determined with hsCRP levels. *Methods:* A total of 184 participants with DM2 (of them 47.3% females) were recruited in this cross-sectional study. Fasting glucose, glycated hemoglobin, lipid parameters and hsCRP were measured. Anthropometric parameters were obtained. Participants were stratified into low (hsCRP <1 mg/L), intermediate (1 mg/L≤ hsCRP <3 mg/L) and high risk CVD category subgroup (hsCRP ≥3 mg/L). *Results:* Significantly higher number of females were in the high hsCRP subgroup, compared with males (χ^2=12.80, p<0.001). Also, significantly higher number of obese individuals were in the high risk subgroup compared with low risk subgroup (χ^2= 18.68, p<0.001). Multiple linear regression analysis showed that waist circumference (WC) (Beta=0.205, p=0.045) and glucose (Beta=0.305, p=0.003) in males, and WC in females (Beta=0.405, p=0.003), were the independent predictors of hsCRP levels. *Conclusion:* Females exhibited higher CVD risk than males, as measured with hsCRP. Also, unlike some other anthropometric indices, WC is independently associated with hsCRP in both gender, suggesting that this simple parameter could be a reliable and cost-effective tool for evaluating CVD risk in population with DM2.

Key words: C-reactive protein, diabetes, inflammation, obesity, waist circumference

Introduction

Inflammation is regarded to be the underlying pathophysiological mechanism in many metabolic disturbances such as metabolic syndrome (1), non-alcoholic fatty liver disease (2), polycystic ovarian syndrome (3), type 2 diabetes mellitus (DM2) (4), and cardiovascular disease (CVD) (5). Since obesity is an established risk factor for the occurrence of all these disorders, it is suggested that inflammation may be the link between hyperthrophied adipose tissue and a broad spectrum of metabolic disturbances (6, 7).

Namely, it was shown that adipose tissue is an endocrine organ that secrets a wide range of pro-inflammatory cytokines and adipokines, thus leading to increased chronic low-grade inflammation state (6). Inflammation may, at the same time, be a contributing factor to both, insulin resistance and endothelial dysfunction, which may also explain the high risk of CVD in individuals with diabetes (6).

Although males are regarded to have a greater risk of CVD than females (8), some studies report that this gender difference gets lost in patients with DM2 (9, 10). In addition, considering the fact that majority of indi-

viduals with DM2 are with overweight or obesity (11), it is not well elucidated which one anthropometric parameter could be the best predictor of unfavorable cardiometabolic profile given the contradictory results of various studies in different population groups (12-15).

Since there is a high prevalence of obesity and DM2 in Montenegro (7, 16), we aimed to examine the association of high sensitivity C-reactive protein (hsCRP) with anthropometric and metabolic parameters in the cohort of Montenegrin adults with DM2. Additionally, we aimed to examine the gender difference in CVD risk as determined with hsCRP levels.

Materials and Methods

Study population

A total of 184 individuals with DM2 (of them 47.3% females) who volunteered to participate in this cross-sectional study were enrolled. Patients with DM2 were consecutively recruited by the endocrinologist in the Primary Health Care Center in Podgorica, Montenegro, for their regular check-up in a period from March 2018 to September 2018.

Inclusion criterion for participation in the study was DM2. Diabetes cases were defined using criteria of American Diabetes Association (17).

Exclusion criteria were: participants with a previous history of CVD, type 1 diabetes mellitus, acute inflammatory disease, hsCRP > 10 mg/L, malignancy, hepatic disease other than steatosis, kidney disease except for diabetic nephropathy, pregnancy, alcohol consumption, usage of anti-inflammatory medicines in the last 6 months, as well as participants who were unwilling to enter the study.

All the participants provided written informed consent. The study protocol was approved by the Institutional Review Board of Primary Health Care Center in Podgorica, Montenegro and the research was carry out following the principles of the Declaration of Helsinki.

Anthropometric measurements

Basic anthropometric measurements: waist circumference (WC) (cm), body height (cm), and body weight (kg) were obtained, and body mass index (BMI) was calculated.

Participants with $18.5 \leq BMI < 25$ kg/m^2, $25 \leq BMI < 30$ kg/m^2 and $BMI \geq 30$ kg/m^2, were regarded as subjects who were normal weight, subjects with overweight and with obesity, respectively. There were no underweight participants in our study (i.e., $BMI < 18.5$ kg/m^2).
Skinfold (SF) thicknesses were measured on four sites with a Harpenden calliper (i.e., at biceps, triceps, iliac, and subscapular sites). All readings were measured to the nearest mm and by the same examiner.

Biochemical analyses

The blood samples were taken between 7-9 hours a.m., after at least 12 hours of fast. Samples were centrifuged at 3000 rpm for 10 minutes, after clotting for 30 minutes. Serum samples were then immediately analyzed. Another aliquot was collecting as a whole blood in K_2EDTA for determination of glycated hemoglobin (HbA1c). Levels of hsCRP and Hba1c were determined immunoturbidimetrically (Roche Cobas c501 analyzer, Mannheim, Germany), whereas levels of glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), and triglycerides (TG), were measured spectrophotometrically on the same analyzer. Low density lipoprotein cholesterol (LDL-c) was calculated using Friedewald formula, as follows: LDL-c = TC - HDL-c - TG / 2.2 (18). Non-HDL-c was calculated as follows: Non-HDL-c = TC - HDL-c. Additionally, TG/HDL-ratio was calculated, also.

Since we aimed to test the association of anthropometric and metabolic parameters with the hsCRP, as well as with CVD risk, all participants were stratified into low (hsCRP <1 mg/L), intermediate (1 mg/L≤ hsCRP <3 mg/L) and high CVD risk category subgroup (hsCRP ≥3mg/L) (19).

Statistical analysis

Statistical package SPSS (version 15.0 for Windows, SPSS, Chicago, IL, USA) was used for statistical analyses. Data are presented as mean ± standard deviation (if normally distributed), median (interquartile range) (if non-normally distributed), or with counts and percentages (categorical variables). Student's t test or one-way ANOVA (for normally), Mann-Whitney test and Kruskal-Wallis non-parametric analysis of variance (for non-normally distributed parameters), were used for the evaluation of differences between

examined groups. The differences between categorical data were analyzed with Chi-squared test. All variables with skewed distribution were logarithmically transformed. The relationship between log hsCRP and other variables was determined with Pearsons's (r) correlation coefficient. Multiple linear regression analysis was performed to identify independent variables affecting log hsCRP. In all analyses p value of < 0.05 was regarded to be statistically significant.

Results

Table 1 shows the general demographic, clinical and biochemical characteristics of the studied participants with diabetes. With exception to WC (p=0.708), females displayed significantly higher anthropometric indices [i.e., BMI (p=0.001) and all four skinfold thickness measures (p<0.001, respectively)]. Also, females had higher TC (p=0.005), HDL-c (p<0.001), TG/HDL-ratio (p=0.056), as well as hsCRP (p=0.004). More males than females were on insulin therapy (p=0.008) and were classified as smokers (p=0.042), whereas more females were on antihypertensive therapy (p=0.046), and were classified as obese (p=0.005). There was no gender difference in age, fasting glucose, HbA1c, LDL-c, non-HDL-c, TG, oral antihyperglycemic and hypolipidemic therapy usage, as well as in duration of diabetes, between the groups (Table 1).

Significantly higher number of females were in the high hsCRP subgroup, compared with males (χ^2=12.80, p<0.001). Also, significantly higher number of obese individuals were in the high risk subgroup as compared with low risk subgroup (χ^2=18.68, p<0.001). Furthermore, we found significantly higher values of all examined anthropometric parameters [e.g., BMI and WC (p<0.001, respectively), SF biceps, SF triceps, SF suprailiac and SF subscapular thicknesses (p=0.003, p=0.002, p=0.026 and p=0.003, respectively)] in the high risk subgroup, compared to low and intermediate subgroup (Table 2).

Pearson's correlation analysis was performed in order to examine potential relationship between hsCRP and anthropometric and metabolic parameters in participants with DM2. As shown, hsCRP correlated positively with anthropometric parameters (i.e., BMI and WC) and fasting glucose both, in males and females. Also, hsCRP correlated positively with age, SF subscapular thickness and TG/HDL-c ratio only in females (Table 3).

All variables that showed a significant predictive value in Pearson's correlation (i.e., WC and glucose in both gender, and age, SF subscapular thick-

Table 1. General characteristics of studied participants with diabetes

Characteristics	Women (n=87)	Men (n=97)	p
Age (years)	63.2±10.9	61.3±11.3	0.233
BMI (kg/m²)#	30.1 (27.7-33.9)	28.3 (26.0-30.9)	0.001
WC (cm)	107±11.7	106±12.0	0.708
SF biceps (mm)#	18.0 (15.0-22.0)	12.0 (8.0-15.0)	<0.001
SF triceps (mm)#	26.5 (21.0-32.0)	13.0 (10.0-18.7)	<0.001
SF suprailiac (mm)	33.9±6.22	29.8±9.20	<0.001
SF subscapular (mm)	33.1±6.63	27.6±8.59	<0.001
Fasting glucose (mmol/L)	7.72±2.20	8.51±3.30	0.414
HbA1c (%)#	6.50 (5.80-7.67)	6.70 (5.80-8.10)	0.339
TC (mmol/L)#	5.43 (4.86-6.27)	5.07 (4.41-5.70)	0.005
HDL-c (mmol/L)#	1.29 (1.10-1.51)	1.01 (0.84-1.32)	<0.001
LDL-c (mmol/L)#	3.28 (2.77-3.95)	3.02 (2.49-3.68)	0.148
TG (mmol/L)#	1.83 (1.47-2.45)	1.82 (1.28-2.49)	0.897
Non-HDL-c (mmol/L)#	4.19 (3.47-5.00)	3.93 (3.33-4.71)	0.150
TG/HDL-c ratio#	1.41 (0.94-2.30)	1.89 (1.07-2.63)	0.056
hsCRP (mg/L)	1.98 (1.10-4.79)	1.42 (0.76-2.46)	0.004
Smoking habits (No/Yes), n (%)	73/14 (83.9/16.1)	68/29 (70.1/29.9)	0.042
Antihypertensives (No/Yes), n (%)	18/69 (20.7/79.3)	34/63 (35.1/64.9)	0.046
Hypolipidemics (No/Yes), n (%)	49/38 (56.3/43.7)	55/42 (56.7/43.3)	0.923
Antihyperglycemics (No/Yes), n (%)	6/81 (6.9/93.1)	15/82 (15.5/84.5)	0.138
Insulin (No/Yes), n (%)	78/9 (89.7/10.3)	71/26 (73.2/26.8)	0.008
Duration of diabetes (years)#	4.00 (2.00-7.75)	5.00 (2.00-10.00)	0.259
Normal weight/ Overweight/Obese, n (%)	6/35/46 (6.9/40.2/52.9)	15/49/33 (15.5/50.5/34.0)	0.005

Data are presented as mean ± standard deviation or # median (interquartile range), or counts (percentages); BMI-Body mass index; WC-Waist circumference; SF-skinfold thickness; HbA1c-glycated hemoglobin; TC-Total cholesterol; HDL-c-High density lipoprotein cholesterol; LDL-c-Low density lipoprotein cholesterol; TG-Triglycerides; hsCRP-high sensitivity C-reactive protein

Table 2. Anthropometric and metabolic parameters in subgroups according to cardiovascular risk level, as estimated with hsCRP

Parameter	Low risk group (hsCRP < 1 mg/L), n=54 (29.4 %)	Intermediate risk group (1 ≤ hsCRP <3 mg/L), n=77 (41.8 %)	High risk group (hsCRP ≥ 3 mg/L), n=53 (28.8 %)	p
Age (years)	63.7±9.99	61.7±10.09	61.4±13.49	0.483
BMI (kg/m²)#	27.7 (25.2-30.2)^{aaa,b}	28.7 (27.2-31.7)^{aa}	28.6±3.68	<0.001
WC (cm)	100±11.1^{aaa,b}	105±10.6^{aa}	111±12.4	<0.001
SF biceps (mm)#	13.0 (8.3-17.8)^{aa,b}	14.0 (11.0-19.8)	17.0 (13.0-22.0)	0.003
SF triceps (mm)#	14.0 (10.3-22.5)^{aa,b}	20.0 (13.3-26.8)	24.0 (14.3-30.0)	0.002
SF suprailiac (mm)	29.4±9.74^{a}	32.0±7.15	33.7±7.51	0.026
SF subscapular (mm)	27.4±8.33^{aa,b}	30.2±7.70	32.8±7.98	0.003
Glucose (mmol/L)	7.08±1.50	8.00±2.63	8.52±3.42	0.513
HbA1c (%)#	6.50 (5.77-7.87)	6.70 (5.77-8.00)	6.60 (5.97-7.70)	0.598
TC (mmol/L)#	5.20 (4.74-5.78)	5.22 (4.55-6.00)	5.26 (4.56-6.12)	0.812
HDL-c (mmol/L)#	1.21 (0.92-1.52)	1.14 (0.93-1.37)	1.18 (0.93-1.30)	0.598
LDL-c (mmol/L)#	3.00 (2.63-3.75)	3.14 (2.55-3.89)	3.10 (2.62-3.93)	0.869
TG (mmol/L)#	1.68 (1.26-2.13)	1.86 (1.39-2.56)	2.11 (1.49-2.91)	0.177
Non-HDL-c (mmol/L)#	4.04 (3.45-4.68)	4.03 (3.28-4.84)	4.11 (3.35-5.02)	0.667
TG/HDL-c ratio#	1.31 (0.98-2.33)	1.58 (0.99-2.54)	1.91 (1.18-2.57)	0.317
Duration of diabetes (years)#	5.50 (2.00-10.00)	4.00 (2.00-8.00)	4.00 (1.75-7.00)	0.290
Normal weight, n (%)	11 (20.4)	6 (7.8)	4 (7.5)	**χ2= 18.68** <0.001
Overweight, n (%)	26 (48.1)	43 (55.8)	15 (28.3)	
Obese, n (%)	17 (31.5)	28 (36.4)	34 (64.2)	
Gender (F/M), n (%)	16/38 (29.6/70.4)	37/40 (48.1/51.9)	34/19 (64.2/35.8)	χ^2= 12.80 <0.001

*^{a} – p<0.05, ^{aa} – p<0.01, ^{aaa} -p<0.001 vs. High risk group, ^{b} – p<0.05, ^{bb} – p<0.01, ^{bbb} – p<0.001 vs. Medium risk group. #- data with non-Gaussian distribution are shown as median values (interquartile range) *P value from one-way ANOVA or Kruskal-Wallis non-parametric analysis of variance, followed by Student's t-test or non-parametric Mann-Whitney U test, where appropriate; BMI-Body mass index; WC-Waist circumference; SF-skinfold thickness; HbA1c-glycated hemoglobin; TC-total cholesterol; HDL-c-High density lipoprotein cholesterol; LDL-c-Low density lipoprotein cholesterol; TG-Triglycerides; hsCRP-High sensitivity C–reactive protein; F-Females; M-Males*

ness and TG/HDL-c ratio only in females) were further analyzed in multiple linear regression analysis analysis for hsCRP prediction. The backward selection enabled to find the best model consisted of 2 parameters [e.g., WC (Beta=0.205, p=0.045 and glucose (Beta=0.305, p=0.003)] in males, and only WC in females (Beta=0.405, p=0.003), (Table 4).

Discussion

The finding of the current study shows that females with DM2 have higher inflammation level, as well as higher CVD risk than males, as assessed with hsCRP. Furthermore, hsCRP is significantly associated with anthropometric indices in patients with DM2, but central adiposity, as measured with WC is its better predictor, compared to general adiposity measure (e.g., BMI) and four skinfold thickness measures (e.g., biceps, triceps, subscapular and suprailiac) in individuals with DM2 (Table 4).

We previously showed that WC was the independent predictor of hsCRP level in normal weight and overweight, otherwise healthy postmenopausal women (7), and that WC correlated better than BMI with cardiometabolic parameters even in younger healthy population (20, 21). Current study extends those observations, suggesting that this simple and

Table 3. Pearson's correlation coefficients (r) of log hsCRP with studied parameters

Variable	Females r	p	Males r	p
Age (years)	-0.233	0.030	0.038	0.709
BMI (kg/m²)	0.549	<0.001	0.193	0.058
WC (cm)	0.496	<0.001	0.200	0.050
SF biceps (mm)	0.185	0.096	0.065	0.530
SF triceps (mm)	0.192	0.084	-0.023	0.822
SF suprailiac (mm)	0.215	0.053	0.015	0.888
SF subscapular (mm)	0.252	0.022	0.095	0.360
Fasting glucose (mmol/L)	0.286	0.007	0.271	0.007
HbA1c (%)	0.177	0.101	0.139	0.176
TC (mmol/L)	0.104	0.337	-0.154	0.132
HDL-c (mmol/L)	-0.121	0.266	-0.197	0.053
LDL-c (mmol/L)	0.051	0.638	-0.126	0.217
TG (mmol/L)	0.174	0.108	0.025	0.806
Non-HDL-c (mmol/L)	0.146	0.179	-0.123	0.230
TG/HDL-c ratio	0.267	0.012	0.041	0.687
Duration of diabetes (years)	0.022	0.838	-0.092	0.370

BMI-Body mass index; WC-Waist circumference; SF-skinfold thickness; HbA1c-glycated hemoglobin; TC-total cholesterol; HDL-c-High density lipoprotein cholesterol; LDL-c-Low density lipoprotein cholesterol; TG-Triglycerides; hsCRP-high sensitivity C–reactive protein

Table 4. Multiple linear regression analysis for the association of several parameters with log hsCRP as dependent variable

Coefficients					
Model for males	Unstandardized Coefficients		Standardized Coefficients	t	p
	B	Std. Error	Beta		
(Constant)	-8.187	2.925		-2.799	0.006
Glucose (mmol/L)	0.251	0.081	0.305	3.096	0.003
WC (cm)	0.046	0.023	0.205	2.034	0.045

WC-Waist circumference

Coefficients					
Model for females	Unstandardized Coefficients		Standardized Coefficients	t	p
	B	Std. Error	Beta		
(Constant)	-14.020	4.582		-3.060	0.003
WC (cm)	0.107	0.034	0.405	3.134	0.003

WC-Waist circumference

cost-effective anthropometric parameter could be a reliable tool for evaluating CVD risk, not only in healthy, but also in population with diabetes. In addition, a majority of population with diabetes in our study were with overweight/obesity (88.6%), (Table 1), which is in line with previous studies, pointing out obesity as a key determinant for DM2 occurrence and progression (6). Moreover, adipocytes and macrophages from hyperplastic and hypertrophied adipose tissue secrete a broad spectrum of adipokines and pro-inflammatory cytokines [e.g., CRP, Interleukin-6, Tumor necrosis factor-alpha] which impair insulin signaling within the cells and lead to consequent obesity-related comorbidities, such as metabolic syndrome, DM2, CVD (6, 7, 22).

In the current study, about 42% of individuals with DM2 had CRP levels ≥2 mg/L, and about one third (29%) of participants had hCRP levels ≥3mg/L (Table 2), which categorized them in intermediate and high risk category for CVD, respectively (23). Similarly, Halcox et al. (24) reported that approximately 50% of non-diabetic patients had CRP levels ≥2 mg/L, and about 30% had CRP levels ≥3 mg/L. Morever, Salazar et al. (25) observed that individuals with hsCRP >3 mg/L had doubled CVD risk, whereas those with hsCRP 1–3 mg/L displayed 50% higher risk of CVD, compared to those with hsCRP <1 mg/L.

Women with DM2 free of previous known CVD in our study displayed higher hsCRP levels compared to males (Table 1), which is similar to other studies (1, 24), but contrary to another ones (26). These discrepancies may be explained by different sample size of studied groups, as well as different age of participants in those studies. Furthermore, with exception to WC, women in our study had higher anthropometric indices than men. Also, significantly higher number of females with DM2 were in the high hsCRP subgroup, compared with males (Table 2). Although males are regarded to have a greater risk of CVD than females (8), there are studies showing that this gender difference gets lost in patients with DM2 (9, 10). In addition, this gender difference in CVD risk gets diminished in postmenopause, since women in that period tend to have more atherogenic profile, and show redistribution of adipose tissue toward visceral region, compared to women in premenopause (27). The majority of wom-

en in our study were considered to be postmenopausal, and were with obesity, which can explain higher hsCRP, as well as higher CVD risk in females than in males with DM2.

Since this study has cross-sectional design, the causalty between obesity, inflammation and CVD risk in population with diabetes cannot be established. Thus, large-scale longitudinal studies are needed to confirm this possible causalty, as well as to confirm the benefits of reduction of inflammation in decreasing the risk of diabetes complications, such as CVD.

In conclusion, females with DM2 have higher CVD risk, as measured with hsCRP than males. Furthermore, among other examined anthropometric indices, WC is independently associated with hsCRP, both in males and females, suggesting that this simple parameter could be a reliable and cost-effective tool for evaluating CVD risk in population with DM2.

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