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Retinol-binding protein 4 better correlates with metabolic syndrome than cystatin C

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Abstract

Background: Retinol-binding protein 4 (RBP4) and cystatin C are regarded as novel metabolic risk markers. Therefore, we aimed to examine which one of these biomarkers better correlates with metabolic syndrome (MetS) in a cohort of postmenopausal women.

Methods: A total of 129 postmenopausal women (among which 62 women had MetS) were recruited in this cross-sectional study. MetS was diagnosed according to the International Diabetes Federation criteria.

Results: Cystatin C and RBP4 levels were significantly higher in women with MetS, compared to those without MetS ($p=0.011$ vs. $p<0.001$, respectively). A significant difference in the proportion of women with and without MetS across cystatin C and RBP4 quartiles was observed ($\chi^2=5.1$, $p=0.025$, and $\chi^2=11.1$, $p=0.001$, respectively). Logistic regression analysis revealed a borderline significant relationship between cystatin C and MetS ($p=0.066$), but this significance disappeared after adjustment for age, inflammation level and duration of menopause ($p=0.221$). On the contrary, a significant relationship between RBP4 and MetS was observed not only without adjustment ($p=0.009$), but also even after adjustment for age, inflammation level and duration of menopause ($p=0.006$).

Conclusions: RBP4 better correlates with MetS than cystatin C in postmenopausal women.

Keywords: cystatin C; metabolic syndrome; postmenopausal; retinol-binding protein 4.

Introduction

The prevalence of metabolic syndrome (MetS) was found to have increased worldwide, along with the increasing prevalence of obesity and diabetes mellitus type 2 (T2D), and females are more affected than males [1, 2]. This metabolic disorder has a multifactorial origin and is accompanied with an increase in visceral fat, low-grade inflammation, insulin resistance, unfavorable lipid profile, endothelial dysfunction and hypertension [3].

Visceral adiposity is considered to be the hallmark of MetS [1]. Dysregulated expression of the broad spectrum of adipocytokines is responsible for systemic inflammatory state, which contributes to the pathogenesis of MetS, T2D and cardiovascular disease (CVD) [4]. Visceral fat accumulation and MetS incidence among women increase after menopause [4], thus explaining the higher risk of T2D and CVD compared to the premenopausal state.

Retinol-binding protein 4 (RBP4) and cystatin C were shown to be highly expressed in human adipose tissue [5, 6], and were closely related to insulin resistance and inflammation [7, 8]. A few previous studies reported the association between RBP4 [7, 9] and cystatin C [10, 11], respectively, with MetS. However, none of these studies evaluated both of these proteins in order to reveal which one of them might have a stronger association with MetS.

Considering the high prevalence of MetS in postmenopausal women [2], and having in mind that the role of both of these proteins in the postmenopausal state is not well elucidated, we aimed to explore which one of them better correlates with MetS status in this population group.

Materials and methods

Study population

This research was derived from the previous study that examined the relationship between RBP4 and cystatin C with CVD risk in postmenopausal women [12]. The current cross-sectional study enrolled a total of 133 postmenopausal women who were recruited for the examination when visiting the Primary Health Care Center in Podgorica for

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their regular gynecologic check-up, in the period from October 2012 to May 2013. However, due to incomplete data, four women were excluded from further analyses. Therefore, a total number of 129 postmenopausal women (mean age 57.1 ± 4.6 years) were eligible to participate in the study.

Inclusion criteria for participation in the study were described in detail elsewhere [12]. Women were regarded to be postmenopausal if they reported the absence of menstrual bleeding for more than 1 year.

Postmenopausal women who had estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m², high sensitivity C-reactive protein levels (hsCRP) >10 mg/L, CVD, hepatic dysfunction other than steatosis and T2D were excluded from the study, as well as those who used any medications (antihypertensive, lipid-lowering, hypoglycemic, anti-inflammatory medications or hormonal replacement therapy) in the last 6 months [12, 13].

Study participants who met the criteria were asked not to perform any vigorous physical activity the day before blood sampling. All the examinees provided written informed consent. The study protocol was approved by the Ethical Committee of the Primary Health Care Center in Podgorica, Montenegro (number 29/V-16) and the investigation was accomplished in accordance with the Declaration of Helsinki.

Anthropometric measurements

Anthropometric measurements were taken on each participant (i.e. body height [cm], body weight [kg] and waist circumference [WC] [cm]), and body mass index (BMI) (kg/m²) was calculated, as described elsewhere [13]. Afterward, the examinees were divided into two groups: a group of postmenopausal women without MetS ($n=67$) and a group of postmenopausal women with MetS ($n=62$). MetS was established according to the International Diabetes Federation criteria [14]. Participants with WC ≥ 80 cm and at least two or more of the following criteria were diagnosed with MetS: fasting glucose ≥ 5.6 mmol/L; high density lipoprotein cholesterol (HDL-c) ≤ 1.29 mmol/L; triglycerides (TG) ≥ 1.70 mmol/L; hypertension: systolic blood pressure (SBP) or diastolic blood pressure (DBP) $\geq 130/85$ mmHg.

Blood pressure was obtained as previously described [12].

Biochemical analyses

Biochemical analyses were performed as described elsewhere [12]. Serum levels of glucose, creatinine, total

cholesterol (TC), HDL-c, low density lipoprotein cholesterol (LDL-c) and TG were measured using standardized procedures (Roche Cobas 400, Mannheim, Germany). Cystatin C, RBP4 and hsCRP levels were determined using a nephelometric assay (Behring Nephelometer Analyzer, Marburg, Germany). Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) [12].

Statistical analysis

The necessary sample size was calculated using RBP4 and cystatin C in order to detect a difference of about 20% in both parameters between the analyzed groups at a power of 80% and a p-value of 0.05 [15]. The SPSS statistical package (version 15.0 for Windows, SPSS, Chicago, IL, USA) was used for statistical analysis. Data are shown as mean $\pm$ standard deviation, or median (interquartile range) or counts and percentages, after testing their distributions. A Student's t-test for normally or Mann-Whitney test for non-normally distributed parameters were used for testing the differences between groups. The differences between categorical data were analyzed with chi-squared (χ^2) test. Logistic regression analysis was used to test the relationship between MetS status and cystatin C and RBP4, respectively. In all analyses, a p-value of <0.05 was regarded to be statistically significant.

Results

Table 1 shows the general clinical and biochemical features of the examined postmenopausal women divided into those without and with MetS. Compared to those without MetS, women with MetS had higher anthropometric measurements, fasting glucose, TG, SBP and DBP, and lower HDL-c ($p<0.001$), as it would be expected based on the definition of MetS. They also exhibited higher serum hsCRP levels ($p=0.024$). Moreover, women with MetS displayed higher serum cystatin C levels (0.79 ± 0.10 mg/L vs. 0.75 ± 0.09 mg/L, $p=0.011$) and RBP4 levels (45.1 ± 8.64 mg/L vs. 39.4 ± 8.67 mg/L, $p<0.001$) than women without MetS. No significant difference was found with respect to age, TC, creatinine, eGFR and duration of menopause between these two groups.

Table 2 represents Pearson's correlation between cystatin C, RBP4 and cardiometabolic parameters in postmenopausal women. Cystatin C correlated with many

Table 1: General characteristics of the studied women.

Characteristics	Women without MetS (n=67)	Women with MetS (n=62)	p-Value
Age, years	56.4 ± 4.77	57.8 ± 4.38	0.087
BMI, kg/m ²	25.3 ± 3.88	28.8 ± 3.88	<0.001
WC, cm	85.8 ± 10.49	96.1 ± 9.96	<0.001
Glucose, mmol/L	5.20 ± 0.36	5.58 ± 0.60	<0.001
TC, mmol/L	6.36 ± 0.99	6.67 ± 1.10	0.100
HDL-cholesterol, mmol/L ^a	1.81 (1.66–2.07)	1.29 (1.19–1.56)	<0.001
LDL-cholesterol, mmol/L	4.08 ± 0.93	4.63 ± 0.99	0.001
TG, mmol/L ^a	1.07 (0.77–1.34)	1.71 (1.31–2.31)	<0.001
hsCRP, mg/L ^a	0.97 (0.46–1.64)	1.61 (0.64–2.82)	0.024
SBP, mmHg	124 ± 20.4	147 ± 17.2	<0.001
DBP, mmHg	80.2 ± 11.81	93.0 ± 9.12	<0.001
Creatinine, µmol/L	55.2 ± 6.67	56.0 ± 6.20	0.486
eGFR, mL/min/1.73 m ²	101 ± 8.0	90.0 ± 5.7	0.084
Cystatin C, mg/L	0.75 ± 0.09	0.79 ± 0.10	0.011
RBP4, mg/L	39.4 ± 8.67	45.1 ± 8.64	<0.001
Time since menopause, years	6.91 ± 4.94	7.27 ± 4.88	0.545

Data are presented as mean ± standard deviation or ^amedian (interquartile range); MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; TC, total cholesterol; HDL-cholesterol, high density lipoprotein cholesterol; LDL-cholesterol, low density lipoprotein cholesterol; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration Equation; RBP4, retinol-binding protein 4.

Table 2: Pearson's correlation between cystatin C, RBP4 and cardiometabolic parameters.

	Cystatin C		RBP4	
	Pearson's correlation	p-Value	Pearson's correlation	p-Value
Age, years	0.216	0.014	0.088	0.322
BMI, kg/m ²	0.400	0.000	0.055	0.533
WC, cm	0.434	0.000	0.050	0.575
Creatinine, µmol/L	0.428	0.000	0.177	0.044
eGFR, mL/min/1.73 m ²	−0.406	0.000	−0.192	0.029
TC, mmol/L	0.129	0.146	0.246	0.005
HDL-cholesterol, mmol/L	−0.047	0.595	−0.160	0.070
LDL-cholesterol, mmol/L	0.169	0.056	0.247	0.005
Uric acid, µmol/L	0.480	0.000	0.147	0.096
Glucose, mmol/L	0.264	0.003	0.188	0.033
SBP, mmHg	0.309	0.000	0.186	0.035
DBP, mmHg	0.333	0.000	0.182	0.039
Log hsCRP	0.331	0.000	−0.145	0.102
Log TG	0.081	0.361	0.377	0.000
Log menopause duration	0.143	0.107	0.082	0.353

BMI, body mass index; WC, waist circumference; TC, total cholesterol; HDL-cholesterol, high density lipoprotein cholesterol; LDL-cholesterol, low density lipoprotein cholesterol; Log TG, logarithmically transformed triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure; log hsCRP, logarithmically transformed high sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration Equation; RBP4, retinol-binding protein 4.

MetS components (i.e. with WC, fasting glucose, SBP and DBP [$p < 0.001$, $p = 0.003$, $p < 0.001$ and $p < 0.001$, respectively]). Also, RBP4 correlated with many MetS indices (i.e. with log TG, fasting glucose, SBP and DBP [$p < 0.001$, $p = 0.033$, $p = 0.035$ and $p = 0.039$, respectively])).

In the current investigation, we also found a significantly higher number of patients with MetS compared to subjects without diagnosed MetS across cystatin C and RBP4 quartiles ($\chi^2 = 5.1$, $p = 0.025$, and $\chi^2 = 11.1$, $p = 0.001$, respectively) (Table 3). This confirmed, at least partially,

Table 3: Metabolic syndrome distribution in cystatin C and RBP4 value subgroups.

MetS status	Cystatin C quartile values				p-Value
	I quartile ≤0.70 mg/L	II quartile 0.71–0.77 mg/L	III quartile 0.78–0.84 mg/L	IV quartile ≥0.85 mg/L	
MetS+, n (%)	15 (24.2%)	11 (17.7%)	15 (24.2%)	21 (33.9%)	$\chi^2 = 5.05$ p = 0.025
MetS–, n (%)	21 (31.3%)	21 (31.3%)	14 (20.9%)	11 (16.4%)	
	RBP4 quartile values				
	I quartile ≤36 mg/L	II quartile 37–42 mg/L	III quartile 43–48 mg/L	IV quartile ≥49 mg/L	
MetS+, n (%)	10 (16.1%)	14 (22.6%)	19 (30.6%)	19 (30.6%)	$\chi^2 = 11.09$ p = 0.001
MetS–, n (%)	23 (34.3%)	21 (31.3%)	15 (22.4%)	8 (11.9%)	

MetS+, women with metabolic syndrome; MetS–, women without metabolic syndrome.

Table 4: Logistic regression analysis of the association of metabolic syndrome with cystatin C, divided into quartiles.

Cystatin C	Quartiles				p-Value
	1	2	3	4	
No adjustment	1	0.733 (0.274–1.965)	1.500 (0.560–4.015)	2.673 (0.998–7.161)	0.066
Adjustment for age	1	0.675 (0.248–1.838)	1.310 (0.478–3.594)	2.392 (0.878–6.521)	0.097
Adjustment for age, hsCRP, menopause duration	1	0.561 (0.198–1.585)	1.077 (0.380–3.053)	1.706 (0.589–4.940)	0.221

hsCRP, high sensitivity C-reactive protein.

Table 5: Logistic regression analysis of the association of metabolic syndrome with RBP4, divided into quartiles.

RBP4	Quartiles				p-Value
	1	2	3	4	
No adjustment	1	1.533 (0.562–4.186)	2.913 (1.067–7.957)	5.463 (1.799–16.586)	0.009
Adjustment for age	1	1.416 (0.510–3.931)	2.909 (1.053–8.034)	5.279 (1.721–16.197)	0.010
Adjustment for age, hsCRP menopause duration	1	1.755 (0.598–5.147)	2.882 (1.015–8.189)	6.666 (2.077–21.395)	0.006

RBP4, retinol-binding protein 4; hsCRP, high sensitivity C-reactive protein.

the correlation of these two proteins with MetS status in postmenopausal women in our study.

Thereafter, we performed logistic regression analysis to further test the relationship between MetS status and cystatin C and RBP4 (divided into quartile subgroups), respectively.

Logistic regression analysis revealed a borderline significant relationship between cystatin C and MetS (p = 0.066), but this significance disappeared after adjustment for age (p = 0.097), and age, hsCRP and duration of menopause (p = 0.221). On the other hand, a significant relationship between RBP4 and MetS was observed even after adjustment for confounding factors (i.e. age [p = 0.010], and age, hsCRP and duration of menopause [p = 0.006]) (Tables 4 and 5).

Discussion

To our knowledge, there are no studies that compared the utility of RBP4 and cystatin C in relation to MetS status in postmenopausal women. The novel finding of the current study shows that RBP4 correlates with MetS better than cystatin C in postmenopausal women.

Namely, in our study, postmenopausal women with MetS and eGFR within the normal reference range displayed significantly higher RBP4 and cystatin C levels, compared to women without diagnosed MetS. Moreover, we found a significantly higher number of individuals with MetS compared to subjects without diagnosed MetS across cystatin C and RBP4 quartiles. This also confirmed, at least partially, the association of these two

proteins with MetS in postmenopausal women in our study.

Therefore, we further explored the strength of the relationship of these two proteins with MetS status by adjusting for confounding factors, such as age, inflammation (as measured with hsCRP) and duration of menopause. The relationship of MetS with cystatin C was not significant anymore after adjustment for confounding variables, while the relationship with RBP4 was still significant. In the light of these results, we presume that RBP4 may be a better determinant of MetS status than cystatin C in postmenopausal women.

Not only are RBP4 and cystatin C regarded as kidney function markers, but also as adipokines as both of these proteins are highly expressed in human adipose tissue [5, 6], and correlate with obesity-related metabolic disturbances [7, 8]. Indeed, a strong association between RBP4 and MetS was shown by some other studies [7, 9] in subjects of both sex, aged 50–70 years. Namely, a large study of the middle-aged Chinese population reported a progressive increase in RBP4 parallel with the increment in the number of MetS components [9]. Also, in the elderly (in exclusively 75–76-year-old participants), RBP4 concentrations were associated with MetS and its components in both sexes [16].

Studies carried out in young population also suggest the increase of this protein in obese state, insulin resistance and the early stages of MetS [17, 18], whereas some of them showed the association of RBP4 with obesity and MetS components predominantly in boys, rather than in girls [19].

We previously reported RBP4 levels to be the independent predictor of non-alcoholic fatty liver disease, which is regarded as a hepatic manifestation of MetS [13]. Indeed, animal studies have shown that the increase in RBP4 causes insulin resistance and hepatic steatosis and that the latter might occur in parallel with the increase in RBP4 levels within adipose tissue, and earlier than the increase of this adipokine in circulation can be observed [20, 21]. Additionally, the influence of estradiol on the relationship between obesity and circulating RBP4 might also be significant, having in mind that estrogen receptors are abundant in adipose tissue and concerning the findings of recent research of increased RBP4 mRNA levels after incubation of female mouse adipocytes with estradiol [22].

Although in our current study we reported the association between cystatin C and MetS status, this relationship was not significant anymore after adjustment for confounding variables. On the other hand, a prospective Malm Diet and Cancer study [23] reported that high levels of cystatin C can predict MetS, but cystatin C

independently correlated with abdominal obesity, suggesting that the association between cystatin C levels and incident MetS might be mediated by visceral fat.

A study conducted by Liu et al. [24] reported a positive and independent association between higher serum cystatin C levels and the presence of MetS in Chinese premenopausal and postmenopausal women. Furthermore, they reported that elevated cystatin C levels are significantly associated with postmenopausal status [24].

In addition, in animal studies, estrogen has been shown to enhance the expression of cystatin C [25], which all may arise the question of the influence of this sex steroid on cystatin C level in circulation.

Because in our study the association between cystatin C and MetS was attenuated by age, inflammation and duration of menopause, we speculate that factors other than visceral adiposity may be involved in this association. Taking into account that there are no studies examining the influence of sex hormones on cystatin C circulating levels in postmenopausal women, further research is needed to explore this relationship.

The constraints of the present study must be mentioned. Due to the cross-sectional design of this study, the causal relationship between MetS and serum RBP4, as well as cystatin C levels, in postmenopausal women could not be confirmed. However, our study may support the assumption of RBP4 and cystatin C as indicators of metabolic abnormalities in postmenopausal women, but RBP4 was shown to be better associated with MetS status than cystatin C.

Conclusions

To our knowledge, this is the first study of simultaneous examination of RBP4 and cystatin C, in relation to MetS status in postmenopausal women. Postmenopausal women with MetS displayed higher serum RBP4 and cystatin C levels than women without MetS, but RBP4 is better associated with MetS than cystatin C. Further studies are needed to explore potential different mechanisms of their relationship with MetS in this population group.

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References

- Marjani A. A review on metabolic syndrome. *J Endocrinol Metab* 2012;2:166–70.
- Marchi R, Dell'Agnolo CM, Lopes TC, Gravena AA, Demitto MO, Brischiliari SC, et al. Prevalence of metabolic syndrome in pre- and postmenopausal women. *Arch Endocrinol Metab* 2017;61:160–6.
- Kaur J. A comprehensive review on metabolic syndrome. *Cardiol Res Pract* 2014;2014:943162.
- Yamatani H, Takahashi K, Yoshida T, Soga T, Kurachi H. Differences in the fatty acid metabolism of visceral adipose tissue in postmenopausal women. *Menopause* 2014;21:170–6.
- Klötting N, Graham TE, Berndt J, Kralisch S, Kovacs P, Wason CJ, et al. Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. *Cell Metab* 2007;6:79–87.
- Naour N, Fellahi S, Renucci JF, Poitou C, Rouault C, Basdevant A, et al. Potential contribution of adipose tissue to elevated serum cystatin C in human obesity. *Obesity* 2009;17:2121–6.
- Liu Y, Wang D, Li D, Sun R, Xia M. Associations of retinol-binding protein 4 with oxidative stress, inflammatory markers, and metabolic syndrome in a middle-aged and elderly Chinese population. *Diabetol Metab Syndr* 2014;6:25.
- Lee SH, Park SA, Ko SH, Yim HW, Ahn YB, Yoon KH, et al. Insulin resistance and inflammation may have an additional role in the link between cystatin C and cardiovascular disease in type 2 diabetes mellitus patients. *Metabolism* 2010;59:241–6.
- Qi Q, Yu Z, Ye X, Zhao F, Huang P, Hu FB, et al. Elevated retinol-binding protein 4 levels are associated with metabolic syndrome in Chinese people. *J Clin Endocrinol Metab* 2007;92:4827–34.
- Surendar J, Indulekha K, Aravindhan V, Ganesan A, Mohan V. Association of cystatin-C with metabolic syndrome in normal glucose-tolerant subjects (CURES-97). *Diabet Technol Ther* 2010;12:907–12.
- Vigil L, Lopez M, Condes E, Varela M, Lorence D, Garcia-Carretero R, et al. Cystatin C is associated with the metabolic syndrome and other cardiovascular risk factors in a hypertensive population. *J Am Soc Hypertens* 2009;3:201–9.
- Klisic A, Kotur-Stevuljevic J, Kavaric N, Matic M. Relationship between cystatin C, retinol-binding protein 4 and Framingham risk score in healthy postmenopausal women. *Arch Iran Med* 2016;19:845–51.
- Klisic A, Kavaric N, Jovanovic M, Soldatovic I, Gligorovic-Barhanovic N, Kotur-Stevuljevic J. Bioavailable testosterone is independently associated with fatty liver index in postmenopausal women. *Arch Med Sci* 2017;5:1188–96.
- International Diabetes Federation-IDF. The IDF consensus worldwide definition of the metabolic syndrome. Brussels: IDF, 2005.
- Hopkins WG. Estimating sample size for magnitude-based inferences. *Sportscience* 2006;10:63–70.
- Mostafaie N, Sebesta C, Zehetmayer S, Jungwirth S, Huber KR, Hinterberger M, et al. Circulating retinol-binding protein 4 and metabolic syndrome in the elderly. *Wien Med Wochenschr* 2011;161:505–10.
- Robberecht H, Hermans N. Biomarkers of metabolic syndrome: biochemical background and clinical significance. *Metab Syndr Relat D* 2016;14:47–93.
- Chielle EO, Feltez A, Rossi EM. Influence of obesity on the serum concentration of retinol-binding protein 4 (RBP4) in young adults. *J Bras Patol Med Lab* 2017;2:81–6.
- Lin CJ, Chu NF, Hung YJ, Chang JB, He CT, Hsiao FC, et al. The association of retinol-binding protein 4 with metabolic syndrome and obesity in adolescents: the effects of gender and sex hormones. *Clin Pediatr (Phila)* 2013;52:16–23.
- Moraes-Vieira PM, Yore MM, Dwyer PM, Syed I, Aryal P, Kahn BB. RBP4 activates antigen-presenting cells, leading to adipose tissue inflammation and systemic insulin resistance. *Cell Metab* 2014;19:512–26.
- Lee SA, Yuen JJ, Jiang H, Kahn BB, Blaner WS. Adipocyte-specific overexpression of retinol-binding protein 4 causes hepatic steatosis in mice. *Hepatology* 2016;64:1534–46.
- Ameen GI, Mora S. Cbl downregulation increases RBP4 expression in adipocytes of female mice. *J Endocrinol* 2018;236:29–41.
- Magnusson M, Hedblad B, Engström G, Persson M, Nollsson P, Melander O. High levels of cystatin C predict the metabolic syndrome: the prospective Malmö Diet and Cancer Study. *J Intern Med* 2013;274:192–9.
- Liu P, Ma F, Lou H, Zhu Y. Relationship between cystatin C and metabolic syndrome among Chinese premenopausal and postmenopausal women without recognized chronic kidney disease. *Menopause* 2015;22:217–23.
- Slayden OD, Hettrich K, Carroll RS, Otto LN, Clark AL, Brenner RM. Estrogen enhances cystatin C expression in the macaque vagina. *J Clin Endocrinol Metab* 2004;89:883–91.