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BODY MASS INDEX AND INSULIN RESISTANCE AS INDEPENDENT PREDICTORS OF HYPERTENSION IN POSTMENOPAUSAL WOMEN

INDEKS TELESNE MASE I INSULINSKA REZISTENCIJA KAO NEZAVISNI PREDIKTORI HIPERTENZIJE KOD ŽENA U POSTMENOPAUZI

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Sažetak: **Cilj:** Premda su ranije studije potvrdile vezu između gojaznosti i hipertenzije, patofiziološki mehanizam ove povezanosti još uvek nije rasvetljen, naročito što postoje oprečni rezultati kada je u pitanju nezavisna uloga gojaznosti i/ili insulinske rezistencije u nastanku hipertenzije. Stoga je cilj studije bio da se ispita da li je gojaznost [merena indeksom telesne mase (ITM)] prediktor za nastanak hipertenzije, nezavisno od insulinske rezistencije [merene HOMA indeksom (HOMA-IR)] u kohorti žena u postmenopauzi. Metode: Ukupno 150 žena u postmenopauzi koje nisu na terapiji (među njima 44,7% sa hipertenzijom) su uključene u studiju preseka. Antropometrijski i biohemijski parametri, kao i krvni pritisak su mereni. HOMA-IR je računat. **Rezultati:** Multivarijantna logistička regresiona analiza je pokazala da su i ITM (OR=1,240; p=0,035) i HOMA-IR (OR=2,419; p=0,008) nezavisni prediktori krvnog pritiska kod žena u postmenopauzi. Povećanje ITM za 1 kg/m² povećava verovatnoću za pojavu hipertenzije za 24%. Takođe, porast HOMA-IR za 1 jedinicu povećava verovatnoću za pojavu hipertenzije za skoro 2,5 puta. Čak 47% varijacije u vrednosti krvnog pritiska može biti objašnjeno ovim modelom. Takođe, ovaj model je ispravno klasifikovao 76% žena u postmenopauzi koje imaju hipertenziju. **Zaključak:** I gojaznost, i insulinska rezistencija su nezavisni prediktori krvnog pritiska kod žena u postmenopauzi.

Ključne reči: hipertenzija, insulinska rezistencija, gojaznost, žene u postmenopauzi

Abstract: **Aim:** Although previous studies confirmed the association between obesity and hypertension, the underlying pathophysiological mechanism is not well elucidated, specially considering the fact that discordant results exist when examining the independent role of obesity and/or insulin resistance on risk for hypertension onset. Therefore, we aimed to examine if obesity [as measured with body mass index (BMI)] is a predictor for hypertension, independently of insulin resistance [as measured with Homeostasis model assessment of insulin resistance (HOMA-IR)] in the cohort of postmenopausal women. **Methods:** A total of 150 postmenopausal women non-treated with medications (among them 44.7% hypertensive) were included in cross-sectional study. Anthropometric and biochemical parameters, so as blood pressure were obtained. HOMA-IR was calculated. **Results:** Multivariate logistic regression analysis revealed that both, BMI and HOMA-IR were the independent predictors of blood pressure in postmenopausal women (OR=1.240, p=0.035 and OR=2.419, p=0.008, respectively). Rise in BMI for 1 kg/m² enhanced the probability for higher blood pressure by 24%. Also, elevation in HOMA-IR for 1 unit, rose the probability for higher blood pressure almost 2.5 times. Even 47% of variation in blood pressure could be explained with this Model. Also, this Model correctly classified 76% of postmenopausal women having hypertension. **Conclusions:** Both, obesity and insulin resistance are the independent predictors of blood pressure in postmenopausal women.

Keywords: hypertension, insulin resistance, obesity, postmenopausal

INTRODUCTION

It is well known that women experiencing menopause have unfavorable cardiometabolic profile, compared to women in reproductive age [1]. These changes are mostly attributable to hormonal disturbances, mainly due to loss of estrogen [2]. Therefore, it is not surprising that postmenopausal women had higher incidence of cardiometabolic disorders than premenopausal women [1, 3].

It is speculated that redistribution of adipose tissue towards visceral region, due to hormonal changes may be the main pathogenic entity, consequently leading to increased cardiometabolic risk [4] in postmenopause. Increased visceral fat mass is a source of proinflammatory adipocytokines [5-8], exerting a low-grade inflammation environment which could predispose to the future hypertension occurrence [9].

In addition, increased abdominal fat mass is accompanied with increased insulin resistance [4, 8]. However, even though previous studies confirmed the association between obesity and hypertension, the underlying pathophysiological mechanism is not well elucidated [10, 11]. Especially considering the fact that discordant results were seen in literature when examining the independent role of obesity and/or insulin resistance on risk for hypertension occurrence and progression. Namely, some studies reported that obesity may be associated with hypertension incidence, acting through some other mechanisms, different from insulin signaling pathways [10, 11].

Having this in mind, we aimed to examine if obesity [as measured with body mass index (BMI)] has a predictive role for hypertension, independently of insulin resistance [as measured with Homeostasis model assessment of insulin resistance (HOMA-IR)] in the cohort of postmenopausal women.

MATERIALS AND METHODS

Study population

The current cross-sectional study derived from our previous works investigating the utility of examining cardiometabolic markers in postmenopausal women [1-7].

A total of 150 postmenopausal women non-treated with medications (among them 44.7% hypertensive) were included in cross-sectional study. All examined women were recruited by

the gynecologist in the Center of Laboratory Diagnostics of the Primary Health Care Center in Podgorica, Montenegro, for their regular biochemical analyses check-up in a period from October 2012 to May 2013. Women were considered to be postmenopausal if they reported the absence of menstrual bleeding for more than one year.

Inclusion criteria to enter the study were: menopausal status, no signs and symptoms of acute inflammatory disease, no history of malignancy, non-smoking, and no any medicament therapy usage in the last six months.

Exclusion criteria were: High sensitivity C-reactive protein (hsCRP) >10 mg/L, diabetes mellitus, hypothyroidism or hyperthyroidism, liver disease other than steatosis, renal dysfunction, cardiovascular disorders, and any medications use in the last six months.

All postmenopausal women signed informed consent. The investigation was carried out in compliance with the Declaration of Helsinki, and Ethical Committee of Primary Health Care Center in Podgorica, Montenegro approved the study protocol.

Anthropometric measurements

Basic anthropometric measurements were obtained, as described previously [4].

Biochemical analyses

Biochemical parameters were measured as described elsewhere [4]. Serum levels of glucose, lipid parameters [e.g., total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), triglycerides (TG)], bilirubin, uric acid, creatinine, as well as the activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), were measured spectrophotometrically (Roche Cobas 400, Mannheim, Germany).

Levels of hsCRP were determined using an immunonephelometric assay (Behring Nephelometer Analyzer, BN II, Marburg, Germany). HOMA-IR was calculated, as described elsewhere [2]. Blood pressure was measured and Glomerular filtration rate was estimated (eGFR) as described previously [2, 3]. Hypertension was defined as (systolic/diastolic blood pressure (BP) $\geq 140/\geq 90$ mmHg) [9].

Statistical analysis

Statistical data of the study populations are presented as mean \pm standard deviation for

normally distributed data, as geometric means (95% confidence interval - CI) for log-normally distributed data [12] and as median (interquartile range) for skewed distributed data. Distribution of data were tested by Kolmogorov-Smirnov statistical test. Comparisons of continuous normally and log-normally distributed variables were performed using the Student's t-test. Comparisons of skewed distributed data were performed using Mann-Whitney U-test. Spearman's correlation analysis was employed to estimate possible associations of SBP and DBP with general and clinical parameters. Binary logistic regression analysis was performed to assess the ability of demographic and clinical parameters to predict hypertension in postmenopausal women. Postmenopausal women with arterial tension defined as SBP \geq 140 mmHg and DBP \geq 90 mmHg were coded as 1 and postmenopausal women with arterial tension defined as SBP $<$ 140 mmHg and DBP $<$ 90 mmHg were coded as 0. Multivariate logistic regression was performed for Model taking into account all parameters (predictors) that showed significant Spearman bivariate correlation with SBP and DBP. In Model odds (OR) and 95% CI were determined for each parameter. The explained variation in

blood pressure was given by Nagelkerke R² coefficient of logistic regression analysis. Receiver operating characteristic (ROC) curve analysis for Model was performed to assess the ability of tested parameters to discriminate menopausal women with or without hypertension. Hosmer-Lemeshow rule for logistic models was used to test if there was a linear relationship between the predictor variables and the log-odds of the criterion variable (blood pressure level). The areas under the curve (AUC) were defined as poor ($0.5 \leq$ AUC $<$ 0.7), satisfactory ($0.7 \leq$ AUC $<$ 0.8), good ($0.8 \leq$ AUC $<$ 0.9) and excellent (AUC \geq 0.9) [13]. All statistical analyses were performed using PASW Statistics Version 18.0 and MedCalc version 15.8. All statistical tests were considered when probability level was less than 0.05.

Results

The general demographic characteristics of the two study populations are given in Table 1. There were statistical significant differences in all parameters except for menopause duration. Hypertensive menopausal women were older, had higher BMI, WC, SBP and DBP than normotensive menopausal women.

Table 1. General and clinical characteristics of postmenopausal women according to blood pressure
Tabela 1. Opšte i kliničke karakteristike ispitivanih žena u postmenopauzi podjeljenih na osnovu vrednosti krvnog pritiska

	Normotensive	Hypertensive	p
N	83	67	
Age, years	55.87 \pm 4.79	57.55 \pm 4.76	0.033
BMI, kg/m ²	24.75 \pm 3.64	28.58 \pm 4.19	$<$ 0.001
WC, cm *	85.00 (78.00-91.00)	97.00 (85.00-103.00)	$<$ 0.001
SBP, mmHg	110 \pm 17	150 \pm 13	0.005
DBP, mmHg	75 \pm 10	96 \pm 8	0.001
Menopausal duration, years	5.55 \pm 4.81	6.49 \pm 4.66	0.230

Data are presented as arithmetic mean \pm SD and compared with Student's t-test.

*Data are presented as median (interquartile range) and compared by Mann-Whitney U test
BMI-Body mass index; WC-Waist circumference; SBP-Systolic blood pressure; DBP-Diastolic blood pressure

A significantly higher concentration of TC, LDL-c, TG, glucose, insulin, HOMA-IR, creatinine, uric

acid and hsCRP were evident in the group of hypertensive than in normotensive postmenopausal women. On the contrary, HDL-c concentration and eGFR were significantly lower in hypertensive postmenopausal women. There were no significant differences between normotensive and hypertensive women when AST, ALT, ALP and GGT activities, total bilirubin and fibrinogen concentrations were compared between tested groups (Table 2).

Table 2. Laboratory and clinical parameters of studied postmenopausal women
Tabela 2. Laboratorijski i klinički parametri ispitivanih žena u postmenopauzi

	Normotensive	Hypertensive	P
TC, mmol/L	6.29±1.02	6.69±1.06	0.020
HDL-c, mmol/L	1.80±0.44	1.56±0.35	<0.001
LDL-c, mmol/L	4.05±0.97	4.62±1.01	0.001
TG, mmol/L*	1.14 (1.04-1.26)	1.50 (1.36-1.67)	<0.001
Glucose, mmol/L**	5.20 (4.92-5.47)	5.40 (5.10-5.97)	0.005
Insulin, µU/L*	5.21 (4.73-5.75)	8.28 (7.38-9.30)	<0.001
HOMA-IR*	1.21 (1.09-1.34)	2.01 (1.78-2.28)	<0.001
AST, U/L**	18 (17-22)	17 (15-19)	0.100
ALT, U/L**	18 (14-22)	18 (14-24)	0.647
GGT, U/L**	11 (9-15)	12 (9-16)	0.307
Total bilirubin, µmol/L**	7.9 (6.3-11.00)	7.30 (6.82-7.70)	0.124
Creatinine, µmol/L**	54.00 (48.25-59.00)	58.00 (50.25-62.75)	0.038
eGFR, mL/min/1.73m ²	102.53±7.97	98.96±6.58	0.004
Uric acid, µmol/L	242.11±58.79	286.75±63.57	<0.001
HsCRP, mg/L*	0.79 (0.63-0.98)	1.30 (1.03-1.65)	0.002
Fibrinogen, g/L**	3.60 (3.40-4.17)	3.90 (3.42-4.40)	0.127

Data are presented as arithmetic mean ± SD and compared with Student's t-test

*Log-normal distributed data are presented as geometric mean (95% CI) and compared with Student's t-test after logarithmic transformation

** Skewed distributed data are presented as median (interquartile range) and compared with Mann-Whitney U test

TC-Total cholesterol; HDL-c-High density lipoprotein cholesterol; LDL-c-Low density lipoprotein cholesterol; TG-Triglycerides; HOMA-IR-Homeostasis model assessment of insulin resistance; AST-Aspartat

aminotransferase; ALT-Alanine aminotransferase; GGT-Gamma-glutamyl transferase; eGFR-Estimated glomerular filtration rate; hsCRP-High-sensitivity C-reactive protein

According to Spearman's non-parametric correlation analysis significant positive correlations were determined between both, SBP and DBP, with age, BMI, WC, TC, LDL-c, TG, glucose, insulin, HOMA-IR, uric acid and hsCRP (Table 3). Significant negative correlations were determined between both, SBP and DBP, and HDL-c, AST and eGFR.

Table 3. Associations between SBP, DBP and other clinical parameters
Tabela 3. Povezanost između sistolnog, dijastolnog krvnog pritiska i kliničkih parametara

	SBP, mmHg		DBP, mmHg	
	ρ	p	ρ	p
Age, years	0.215	0.008	0.266	0.001
BMI, kg/m ²	0.467	<0.001	0.437	<0.001
WC, cm	0.465	<0.001	0.423	<0.001
Menopause duration, years	0.144	0.080	0.132	0.095
TC, mmol/L	0.195	0.017	0.354	<0.001
HDL-c, mmol/L	-0.354	<0.001	-0.363	<0.001
LDL-c, mmol/L	0.345	<0.001	0.357	<0.001
TG, mmol/L	0.385	<0.001	0.369	<0.001
Glucose, mmol/L	0.314	<0.001	0.279	0.001

Insulin, $\mu\text{IU/L}$	0.519	<0.001	0.482	<0.001
HOMA-IR	0.535	<0.001	0.504	<0.001
AST, U/L	-0.237	0.003	-0.197	0.016
ALT, U/L	0.075	0.363	0.043	0.606
GGT, U/L	0.143	0.080	0.092	0.263
Total bilirubin, $\mu\text{mol/L}$	-0.151	0.066	-0.143	0.081
Creatinine, $\mu\text{mol/L}$	0.156	0.056	0.153	0.061
eGFR, mL/min/1.73m^2	-0.259	0.001	-0.267	0.001
Uric acid, $\mu\text{mol/L}$	0.383	<0.001	0.362	<0.001
HsCRP, mg/L	0.284	<0.001	0.232	0.004
Fibrinogen, g/L	0.125	0.129	0.097	0.236

ρ – Spearman's correlation coefficient

BMI-Body mass index; WC-Waist circumference; TC-Total cholesterol; HDL-c-High density lipoprotein cholesterol; LDL-c-Low density lipoprotein cholesterol; TG-Triglycerides; HOMA-IR-Homeostasis model assessment of insulin resistance; AST-Aspartat aminotransferase; ALT-Alanine aminotransferase; GGT-Gamma-glutamyl transferase; eGFR-Estimated glomerular filtration rate; hsCRP-High-sensitivity C-reactive protein

Multivariate logistic regression analysis was used to establish the independent associations of blood pressure and tested parameters which showed significant correlations with SBP and DBP (Table 4). Those predictors were age, BMI, WC, TC, HDL-c, LDL-c, TG, HOMA-IR, AST, eGFR, uric acid, and hsCRP. Hosmer-Lemeshow rule for logistic models showed that there was a linear relationship between the predictor variables and the log-odds of the blood pressure levels (Chi-squared value was 8.200, $p=0.414$). Although, glucose and insulin concentrations showed significant correlations with SBP and DBP, they were excluded from multivariate logistic regression analysis because they entered equation for HOMA-IR calculation. Adjusted ORs

for tested parameters were shown in Table 4. BMI and HOMA-IR were shown to be the independent predictors of blood pressure in postmenopausal women (OR=1.240, $p=0.035$ and OR=2.419, $p=0.008$, respectively). Rise in BMI for 1 kg/m^2 enhanced the probability for higher blood pressure by 24%. Also, elevation in HOMA-IR for 1 unit, rose the probability for higher blood pressure almost 2.5 times. Adjusted Nagelkerke R² coefficient for the Model was 0.470, which means that 47% of variation in blood pressure could be explained with this Model. Also, this Model correctly classified 76% of postmenopausal women having hypertension.

Table 4. Odds ratios (OR) after multivariate logistic regression analysis for parameters predicting abilities towards blood pressure

Tabela 4. Statistička verovatnoća nakon multivarijantne logističke regresione analize za predikciju krvnog pritiska

Predictors	Adjusted OR (95%CI)	p
Age, years	1.224 (1.025-1.461)	0.102
BMI, kg/m^2	1.240 (1.015-1.515)	0.035
WC, cm	0.922 (0.851-1.012)	0.080
TC, mmol/L	0.543 (0.099-2.981)	0.483

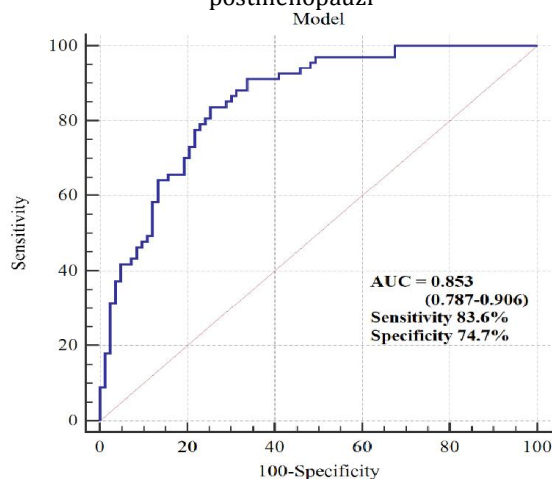
HDL-c, mmol/L	0.525 (0.069-3.995)	0.534
LDL-c, mmol/L	2.707 (0.489-14.991)	0.254
TG, mmol/L	1.175 (0.463-2.980)	0.753
HOMA-IR	2.419 (1.266-4.623)	0.008
AST, U/L	0.865 (0.700-1.095)	0.275
eGFR, mL/min/1.73m ²	1.014 (0.942-1.091)	0.716
Uric acid, μmol/L	1.008 (0.999-1.017)	0.072
HsCRP, mg/L	1.136 (0.861-1.500)	0.367

BMI-Body mass index; WC-Waist circumference; TC-Total cholesterol; HDL-c-High density lipoprotein cholesterol; LDL-c-Low density lipoprotein cholesterol; TG-Triglycerides; HOMA-IR-Homeostasis model assessment of insulin resistance; AST-Aspartate aminotransferase; eGFR-Estimated glomerular filtration rate; hsCRP-High-sensitivity C-reactive protein

ROC analysis was used to discriminate postmenopausal women with hypertension from normotensive ones. When the Model tested in multivariate logistic regression analysis was used in ROC analysis, the clinical accuracy for diagnostic procedure was good (AUC=0.853; 95%CI 0.787-0.906; SE= 0.030). As well, this diagnostic procedure had sensitivity of 83.6% and specificity of 74.7% (Figure 1).

Figure 1. ROC curve of Model discriminating ability between normotensive and hypertensive postmenopausal women

Slika 1. ROC kriva Modela za sposobnost diskriminacije između normotenzivnih i hipertenzivnih žena u postmenopauzi



Discussion

Our study demonstrated that non-treated hypertensive postmenopausal women had higher anthropometric indices (Table 1), unfavorable lipid profile and HOMA-IR, as well as higher inflammation level (Table 2) as compared with normotensive counterparts. In addition, those women displayed higher uric acid level and lower level of eGFR (Table 2). However, multivariate logistic regression analysis revealed that both, BMI and HOMA-IR were the independent predictors of blood

pressure in postmenopausal women (OR=1.240, $p=0.035$ and OR=2.419, $p=0.008$, respectively), (Table 4). Rise in BMI for 1 kg/m² enhanced the probability for higher blood pressure by 24%. Also, elevation in HOMA-IR for 1 unit, rose the probability for higher blood pressure almost 2.5 times. In addition, even 47% of variation in blood pressure could be explained with this Model. Also, this Model correctly classified 76% of postmenopausal women having hypertension,

which is of great importance concerning the fact that hypertension is often undiagnosed and untreated, leading to serious health consequences [14].

Furthermore, ROC analysis was used to discriminate postmenopausal women with hypertension from normotensive ones. When the Model tested in multivariate logistic regression analysis was used in ROC analysis, the clinical accuracy for diagnostic procedure was good (AUC=0.853). As well, this diagnostic procedure had sensitivity of 83.6% and specificity of 74.7% (Figure 1).

Contradictory research results were observed when examining the independent role of obesity and/or insulin resistance on risk for hypertension. Namely, some studies reported independent relationship between obesity and hypertension incidence, acting through some other mechanisms, different from insulin signaling pathways [10, 11]. In line with this, Faria et al. [10] demonstrated the association between visceral fat and blood pressure, whereas No relationship between blood pressure levels and HOMA-IR was shown. Similar results were obtained from the study conducted by Lytsy et al. [15] in the cohort of middle-aged and elderly men, confirming that overweight/obesity without insulin resistance increases the risk of hypertension.

On the other hand, our results are similar with the results of Ben Ali et al. [11], which reported the independent influence of both obesity and HOMA-IR on blood pressure in postmenopausal women.

Insulin resistance as the link between obesity and hypertension is well established, since hyperinsulinemia may enhance sympathetic activity and sodium tubular reabsorption [8, 16]. However, some other mechanisms, different from insulin signaling pathways have been also proposed to cause hypertension development [17, 18]. One possible mechanism lays in the explanation that sodium retention may result from disturbances in the kidney tissue, due to a compressive effect of the enlarged visceral fat [19]. This further results in an hyperactivity of the renin angiotensin system and consequent increase in sodium reabsorption. This hypothesis is further supported by some studies which demonstrated a significant relationship between the amount of visceral fat and systolic blood pressure [10].

Furthermore, some studies suggest that the presence of a low-grade inflammation could predict the future onset of hypertension [9]. Lukic et al. [9] showed that increases in inflammation might be an important factor influencing the occurrence of hypertension in obese patients with diabetes, but which was associated with the rise in interleukin-6 (IL-6).

Another pathogenic mechanism of hypertension onset may be attributed to the role of arterial stiffening which precedes the hypertension occurrence [20]. In this regard, it was suggested that low-grade inflammation may contribute to arterial stiffness, since the impairments in pulse wave velocity, a measure of large vessels distension ability, were correlated with the increases in circulating levels of IL-6 and tumor necrosis factor (TNF)- α [21, 22]. Furthermore, there are assumptions that pro-inflammatory cytokines may exert a direct pathogenic influence on vascular tone regulation leading to the hypertension development [23].

In our study, hypertensive postmenopausal women displayed higher level of inflammation (as measured with hsCRP), and it correlated well with both systolic and diastolic blood pressure in Spearman's non-parametric correlation analysis (Table 3). However, this association was dependent on both, BMI and HOMA-IR in our study (Table 4).

Indeed, exogenous administration of TNF- α or IL-6 resulted in enhanced insulin resistance, suggesting that many cytokines may act in synchrony manner to induce this process [23]. In addition, enlarged adipose tissues is significant contributor of increased pro-inflammatory cytokines in circulation [4, 5, 8], thus further leading to decreased insulin sensitivity.

A small sample size and cross-sectional design are some limitations of our study. However, our cohort comprised of normotensive and non-treated hypertensive postmenopausal women, so we excluded medicines as confounding factors when estimating cardiometabolic profile of hypertensive group. Future longitudinal studies are needed to further explore patophysiological mechanisms related to hypertension onset and to find the best therapeutic target approach for its complications.

Conclusion

Non-treated hypertensive postmenopausal women exerted unfavorable cardiometabolic profile, compared to normotensive counterparts. Both, body mass index and insulin resistance were the independent predictors of blood pressure in postmenopausal women.

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Conflict of Interest Statement

The authors declared no conflicts of interest.

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