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# The serum profile of adipokines in overweight patients with metabolic syndrome

## Stężenie w surowicy krwi adipokin u pacjentów z nadwagą oraz zespołem metabolicznym

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### Abstract

**Introduction:** Obesity is a disease that brings several complications and increases the risk of other diseases like metabolic syndrome, diabetes mellitus type 2, or coronary heart disease. Disturbances in secretion of adipokines caused by obesity have an influence on the development of metabolic complications.

The aim of this study was an investigation of adipokines profile in overweight or obese people with metabolic syndrome in comparison to overweight/obese patients without metabolic syndrome.

**Material and methods:** The studied groups consisted of 38 obese or overweight patients without metabolic syndrome (nonMS) and 17 with recognized metabolic syndrome (MS), according to International Diabetes Federation (IDF) criteria. All individuals underwent anthropometrical and blood-pressure examination as well as biochemical analyses such as: serum concentrations of glucose, insulin, adiponectin, resistin, leptin, TNF-$\alpha$, IL-6, hs-CRP, total cholesterol, HDL, and triglycerides.

**Results:** A significantly lower concentration of adiponectin, and a higher concentration of IL-6, was observed in patients with metabolic syndrome (MS) in comparison to nonMS. Moreover, higher concentrations of hs-CRP and TNF-$\alpha$ were observed in patients with metabolic syndrome.

**Conclusions:** A decreased concentration of adiponectin in obese people is an early predictor of metabolic syndrome. A low adiponectin level could be a marker of high risk of cardiovascular disease in obese patients.

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***Key words:*** *metabolic syndrome, obesity, adipokines*

### Streszczenie

**Wstęp:** Wraz z epidemią otyłości rośnie częstość powikłań będących konsekwencją nadmiaru tkanki tłuszczowej. Spowodowane nadwagą, niekorzystne zmiany w sekrecji adipokin przez tkankę tłuszczową, mają wpływ na rozwój powikłań metabolicznych.

Celem pracy była ocena różnic w stężeniu adipokin pomiędzy osobami otyłymi z zespołem metabolicznym, w porównaniu z obiema osobami otyłymi bez zespołu metabolicznego.

**Materiał i metody:** Badaniem objęto 55 osób z nadwagą lub otyłością, u 38 badanych rozpoznano zespół metaboliczny według kryteriów Międzynarodowej Federacji Diabetyków (IDF, *International Diabetes Federation*). Wykonano badania antropometryczne, pomiar ciśnienia tętniczego oraz analizy biochemiczne, takie jak: stężenie w surowicy glukozy, insuliny, adiponektyny, rezystyny, leptyny, TNF-$\alpha$, IL-6, hs-CRP, cholesterolu całkowitego i frakcji HDL oraz triglicerydów.

**Wyniki:** U osób z zespołem metabolicznym, w porównaniu z osobami bez zespołu, zaobserwowano istotnie niższe stężenie adiponektyny, natomiast stężenie IL-6 było istotnie wyższe. Zanotowano też wyższe stężenie hs-CRP i TNF-$\alpha$ u osób z zespołem metabolicznym, różnica ta nie była jednak istotna statystycznie.

**Wnioski:** Niskie stężenie w surowicy adiponektyny u osób otyłych było predyktorem zespołu metabolicznego. Ponadto niskie stężenie adiponektyny może być markerem wysokiego ryzyka chorób sercowo-naczyniowych u otyłych pacjentów.

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***Słowa kluczowe:*** *zespół metaboliczny, otyłość, adipokiny*

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## Introduction

Obesity is a chronic disease that concerns over a billion adult people all over the world. It involves several complications and increases the risk of other diseases like metabolic syndrome, diabetes mellitus type 2, or coronary heart disease [1–3]. Lack of proper diet, lack of physical activity, and socio-cultural and genetic factors have been known as common causes of metabolic syndrome [4]. The newest studies concentrate mostly on such factors as sub-clinical inflammatory process and hormonal activity of adipose tissue [5].

Adipose tissue is a place of synthesis of several metabolically active proteins called adipokines. These proteins play an important role in the regulation of metabolic processes, thus having auto- and paracrine function. What is more, they regulate systemic processes showing typical endocrine activity. Thus, adipose tissue is a significant element of the endocrine system in humans [6–10].

Free fatty acids and adipokines synthesized in adipose tissue have a significant influence on glucose homeostasis. Adipokines are the main regulators of insulin sensitivity and therefore a potential link between obesity and insulin resistance [11, 12]. Disturbances in the secretion of hormones and inflammatory cytokines caused by obesity may have an influence on the development of typical metabolic complications [13].

Adipose tissue in its endocrine function is not a homogenous organ. There are significant differences between subcutaneous and visceral adipose tissue. Synthesized hormones within visceral tissue undergo secretion processes to portal circulation having a direct influence on metabolic processes in the liver. Substances that are produced in subcutaneous adipose tissue are secreted to systemic circulation. Secretion of such cytokines as IL-6 and PAI-1 is much higher in visceral adipose tissue whereas synthesis of leptin, adiponectin, and TNF-$\alpha$ takes place in subcutaneous adipose tissue.

The differences also concern expression of the receptors. In other words, adipose tissue is a heterogeneous organ in which a secretory function depends on its localization [7, 8, 14]. It may be the reason why central obesity, which is typical for metabolic syndrome, has a stronger correlation to the metabolic complications.

The aim of this study was an investigation of adipokines profile in overweight or obese people with metabolic syndrome, in comparison to overweight/obese patients without metabolic syndrome.

## Material and methods

The study was performed on two groups consisting of 38 obese or overweight patients (BMI > 25 kg/m$^2$) without metabolic syndrome (nonMS) and 17 patients with recognized metabolic syndrome (MS), according to International Diabetes Federation (IDF) criteria. To be diagnosed as having metabolic syndrome, patients had to demonstrate abdominal obesity (waist circumference ≥ 94 cm in men and ≥ 80 cm in women) and fulfil at least two out of four criteria, such as:

— triglycerides concentration ≥ 150 mg/dl or treatment of hypertrigliceridaemia;
— concentration of cholesterol of HDL fraction < 40 mg/dl in men and < 50 mg/dl in women or dyslipidaemia treatment;
— systolic blood pressure (SBP) ≥ 130 mm Hg or diastolic blood pressure (DBP) ≥ 85 mmHg or hypertension;
— fasting glucose concentration in plasma ≥ 100 mg/dl or diagnosed type 2 diabetes [15].

Based on interviews and examinations, patients with secondary obesity were excluded from the study. However, women taking oral contraceptives, hormonal replacement therapy, within 6 months of delivery or breastfeeding, and patients with endocrine, mental, malignant or serious internal diseases were excluded.

The patients were interviewed about their lifestyle and diet, and underwent anthropometrical, biochemical measurements and blood-pressure examination.

### *Anthropometrical measurements*

The following measurements were determined:

— body mass (kg), waist circumference (cm), hip circumference (cm);
— BMI (body mass index) — estimated according to the current body mass/height$^2$ [kg/m$^2$]. BMI in the range 25–30 kg/m$^2$ was recorded as overweight, and BMI ≥ 30 kg/m$^2$ was recorded as obese [3];
— WHR (waist to hip ratio) — estimated based on waist to hip circumferences ratio;
— body composition: body fat content (%F) and lean body mass (LBM) was obtained by near-infrared spectroscopy method (NIR) using a Futrex 5000A unit (Gatesburg Inc., USA).

Body mass and height were measured with attested electronic scales with a body-height measuring device.

### *Laboratory assay*

The samples of blood were taken after 12 hours of overnight fasting and the levels of the following compounds were measured in plasma:

— glucose by enzymatic-calorimetric EMAPOL method;
— insulin by MEIA method (microparticle enzyme immunoassay) using units and IMX by Abbott (USA);
— leptin by ELISA method, DRG Germany units and read on a STAT FAX 2200 (USA);
— adiponectin by ELISA method, Linco (USA);

— resistin by ELISA method, Linco (USA);
— TNF-$\alpha$ by ELISA method, Bender MedSystem (Austria);
— hs- CRP by ELISA method, DRG (Germany);
— IL-6 by ELISA method, Bender MedSystem (Austria);
— total cholesterol (TC), triglycerides (TG), and HDL-cholesterol (HDL) by routine methods using a Hitachi 911.

Insulin-resistance HOMA1-IR index was calculated according to the formula: fasting insulin (mU/L) × fasting glucose level (mmol/L): 22.5 [16]. Blood pressure was checked twice, sitting and after at least 15 minutes of relaxation, using a proper sleeve. In this study, an average from the two measurements is given.

### *Statistical analysis*

Statistical analysis was performed using Statistica 7.1 version for Windows (Krakow, Poland). All data were expressed as mean ± standard deviation (SD). Comparisons of the groups were examined by Student's *t*-test. Pearson correlation test was used to determine the relationship between continuous variables. The independent determinations of metabolic syndrome were made using logistic regression analysis. P value $< 0.05$ was considered statistically significant for all analyses.

## Results

The studied population consisted of 55 patients (38 women, 17 men) with a mean age of 38.8 ± 10.2 years (range 19–59) and was divided into two groups:
— the MS group consisted of 38 overweight patients (69%, 24 women, 12 men) with metabolic syndrome
— the non MS group consisted of 17 overweight patients (31%, 11 women, 5 men) without diagnosed metabolic syndrome.

There were 21% overweight, 58% obese (I° or II°), and 21% with extreme obesity in the MS group. Metabolic syndrome was manifested in all patients with extreme obesity (Fig. 1).

The criteria of metabolic syndrome were presented in the following levels:
— lowered concentration of HDL cholesterol 87.0%,
— hypertension 76.3%,
— hypertrigliceridaemia 76.3%,
— hyperglycaemia 26.3%.

As expected, HDL cholesterol and triglyceride concentrations, as well as values of systolic and diastolic blood pressure, were significantly different between the MS and non MS groups. However, no statistically significant differences were observed in concentrations of total cholesterol and LDL cholesterol.

In the MS group, the mean BMI (35.6 kg/m$^2$) and %F (43.1%) were statistically higher when compared to nonMS group (BMI — 29.8 kg/m$^2$; %F — 37.9%) (Table I).

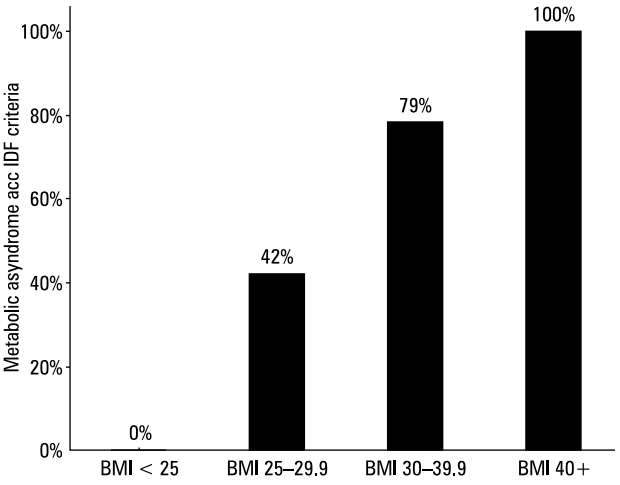


**Figure 1.** *The frequency of metabolic syndrome depend on to BMI*

**Rycina 1.** *Częstość występowania zespołu metabolicznego w zależności od BMI*

**Table I.** ***Anthropometrical parameters and level of blood pressure in the MS and non MS groups***

**Tabela I.** ***Parametry antropometryczne i wartości ciśnienia tętniczego w grupach MS i non MS***

| Parameters | MS (n = 38) | non MS (n = 17) | p |
|---|---|---|---|
| **BMI [kg/m$^2$]** | | | < 0.001 |
| mean ± SD | 35.6 ± 6.1 | 29.8 ± 3.7 | |
| range | 27.2–51.0 | 26.0–38.3 | |
| **F (%)** | | | 0.006 |
| mean ± SD | 43.1 ± 7.5 | 37.9 ± 5.7 | |
| range | 27.9–60.0 | 25.0–49.3 | |
| **F [kg]** | | | < 0.001 |
| mean ± SD | 44.8 ± 14.4 | 31.8 ± 8.3 | |
| range | 25.4–81.0 | 21.3–50.8 | |
| **SBP [mm Hg]** | | | < 0.001 |
| mean ± SD | 134.7 ± 17.3 | 104.1 ± 8.3 | |
| range | 100–170 | 100–132 | |
| **DBP [mm Hg]** | | | < 0.001 |
| mean ± SD | 85.5 ± 10.7 | 71.2 ± 6.0 | |
| range | 60–100 | 60–85 | |

In the MS and non MS groups, the mean insulin concentration was 26.4 $\mu$IU/ml and 14.7 $\mu$IU/ml, with mean HOMA index values of 6.1 and 3.1, respectively. The differences in these parameters of insulin resistance between the groups were statistically significant (Table II).

The MS *v.* non MS patients exhibited significantly lower levels of adiponectin (15 $\mu$g/ml *v.* 20.6 $\mu$g/ml), and significantly higher concentrations of IL-6 (3.2 pg/ml *v.* 2.5 pg/ml) and hs-CRP (8.41 mg/L *v.* 6.5 mg/L). Whereas

**Table II.** *Insulin concentration and HOMA index in the MS and non MS groups*

**Tabela II.** *Stężenia insuliny i wskaźniki HOMA w grupach MS i non MS*

| Parameters | MS (n = 38) | non MS (n = 17) | p |
|---|---|---|---|
| **Insulin [$\mu$IU/ml]** | | | 0.005 |
| mean ± SD | 26.4 ± 18.7 | 14.7 ± 9.1 | |
| range | 8.3–89.0 | 5.5–35.8 | |
| **HOMA** | | | 0.002 |
| mean ± SD | 6.1 ± 4.4 | 3.1 ± 1.9 | |
| range | 1.8–21.4 | 1.1–7.8 | |

the values observed for other analyzed adipokines did not differ between these groups (Table III).

The analysis of logistical regression showed that increased BMI, as well as decreased adiponectin concentration, were the biggest factors stimulating manifestation of metabolic syndrome (Table IV). In univariate analysis, the negative correlations between adiponectin and WHR , insulin and HOMA-IR index value were observed for all studied patients.

In addition, adiponectin correlated positively with HDL cholesterol and negatively with triglyceride levels (Table V) in the whole studied population. Moreover, a negative correlation was observed between adiponectin and SBP as well as DBP ($p < 0.001$ for both variables) (Table VI).

## Discussion

The MS group, in comparison to patients without metabolic syndrome, had higher values of BMI and %F as well, and as expected, higher values of SBP and DBP. Similar results were also observed in other studies [17, 18].

In our studies, patients with recognized metabolic syndrome had almost two times higher values of insulin concentration and HOMA index. In addition, this observation has been confirmed by other authors [18, 19].

The results of our study have shown that patients who fulfilled metabolic syndrome criteria had significantly lower adiponectin levels by about 25% in the MS group. Other authors also described lower adiponectin concentrations in patients with metabolic syndrome (according to both criteria — ATP III and IDF) [20–24].

Body mass index and adiponectin concentration, according to the results of the logistical regression, had a decisive influence on the development of metabolic syndrome. Similarly, Shaibi and others [20] suggested that hypoadiponectinaemia is an independent predictor of metabolic syndrome.

**Table III.** *Biochemical parameters in the MS and non MS groups*

**Tabela III.** *Parametry biochemiczne w grupach MS i non MS*

| Parameters | MS (n = 38) | non MS (n = 17) | p |
|---|---|---|---|
| **hs-CRP [mg/L]** | | | ns (0.190) |
| mean ± SD | 8.4 ± 3.8 | 6.6 ± 4.1 | |
| range | 1.0–10.6 | 1.1–10.6 | |
| **Total cholesterol [mg/dl]** | | | ns |
| mean ± SD | 227 ± 55 | 206 ± 33 | |
| range | 152–452 | 161–283 | |
| **LDL cholesterol [mg/dl]** | | | ns |
| mean ± SD | 144 ± 49 | 130 ± 29 | |
| range | 66–359 | 95–190 | |
| **HDL cholesterol [mg/dl]** | | | < 0.001 |
| mean ± SD | 40.3 ± 8.1 | 56.4 ± 8.6 | |
| range | 27.4–62.0 | 34.9–70.0 | |
| **Triglycerides [mg/dl]** | | | < 0.001 |
| mean ± SD | 203 ± 94 | 97 ± 44 | |
| range | 37–457 | 52–231 | |
| **Adiponectin [$\mu$g/ml]** | | | 0.038 |
| mean ± SD | 15.0 ± 7.2 | 20.6 ± 12.0 | |
| range | 3.1–39.0 | 6.4–46.7 | |
| **Resistin [ng/ml]** | | | |
| mean ± SD | 25.1 ± 17.3 | 25.0 ± 13.9 | ns |
| range | 2.2–70.5 | 8.7–55.7 | |
| **Leptin [ng/ml]** | | | |
| mean ± SD | 7.9 ± 10.5 | 8.3 ± 12.5 | ns |
| range | 0.5–39.5 | 0.5–40.5 | |
| **TNF-$\alpha$ [pg/ml]** | | | |
| mean ± SD | 18.4 ± 13.4 | 12.8 ± 4.6 | ns |
| range | 5–66 | 6–22 | |
| **IL-6 [pg/ml]** | | | |
| mean ± SD | 3.2 ± 0.9 | 2.5 ± 0.4 | 0.012 |
| range | 2–6 | 1.8–3.2 | |

**Table IV.** *Results of logistic regression ($p < 0.001$). The dependence variable: occurrence of metabolic syndrome acc IDF criteria*

**Tabela IV.** *Wyniki regresji logistycznej ($p < 0,001$). Zmienna zależna: występowanie zespołu metabolicznego zdefiniowanego według kryteriów IDF*

| Independent variable | p |
|---|---|
| BMI [kg/m$^2$] | 0.006 |
| Adiponectin [$\mu$g/ml] | 0.017 |
| HOMA* | 0.034 |
| Insulin [$\mu$IU/ml]* | 0.039 |

* — logarithm

**Table V.** *Results of univariate correlation between the studied parameters*

**Tabela V.** *Wyniki korelacji jednozmiennowej pomiędzy badanymi parametrami*

| Total | Cholesterol | LDL Cholesterol | HDL Cholesterol | Triglycerides | TNF-$\alpha$ | IL- 6 | hs-CRP |
|---|---|---|---|---|---|---|---|
| Adiponectin | –0.07 | –0.01 | 0.43*** | –0.27* | –0.26* | –0.14 | –0.18 |
| Resistin | –0.10 | –0.03 | 0.14 | –0.27* | –0.10 | 0.0 | 0.2 |
| Leptin | –0.12 | –0.09 | 0.02 | –0.10 | –0.09 | 0.01 | 0.16 |
| TNF-$\alpha$ | –0.1 | –0.1 | –0.2 | 0.06 | – | 0.2 | –0.19 |
| IL-6 | –0.16 | 0.02 | –0.24 | –0.04 | – | – | 0.14 |
| hs-CRP | 0.05 | 0.21 | –0.15 | –0.1 | – | – | – |

*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001

**Table VI.** *Results of univariate correlation between the studied parameters*

**Tabela VI.** *Wyniki korelacji jednozmiennowej pomiędzy badanymi parametrami*

| | Insulin [$\mu$IU/ml] | HOMA | WHR | Waist circumference [cm] | F (%) | F [kg] | BMI [kg/m$^2$] |
|---|---|---|---|---|---|---|---|
| Adiponectin | –0.45*** | –0.44*** | –0.4** | –0.18 | 0.32 | 0.06 | –0.03 |
| Resistin | –0.10 | –0.09 | –0.25 | 0.07 | 0.15 | 0.22 | 0.17 |
| Leptin | –0.09 | –0.09 | –0.2 | 0.06 | 0.08 | 0.17 | 0.2 |
| TNF-$\alpha$ | 0.19 | 0.2 | 0.10 | 0.02 | –0.21 | –0.10 | –0.06 |
| IL-6 | 0.14 | 0.15 | 0.13 | 0.34** | 0.28* | 0.29* | 0.3* |
| hs-CRP | 0.47*** | 0.43*** | –0.08 | 0.26 | 0.34* | 0.44*** | 0.51*** |
| Total Cholesterol | –0.04 | –0.02 | 0.07 | 0.00 | 0.17 | 0.08 | 0.04 |
| LDL Cholesterol | 0.1 | 0.08 | 0.07 | 0.08 | 0.3* | 0.18 | 0.13 |
| HDL Cholesterol | –0.39** | –0.39** | –0.26 | –0.23 | 0.01 | –0.18 | –0.27* |
| Triglycerides | 0.08 | 0.10 | 0.24 | 0.14 | 0.08 | 0.12 | 0.13 |
| Insulin [$\mu$IU/ml] | – | – | 0.13 | 0.38** | 0.22 | 0.46*** | 0.5*** |
| HOMA | – | – | 0.10 | 0.4 ** | 0.21 | 0.48*** | 0.52*** |

*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001

Adiponectin has a stronger correlation to the possibility of metabolic syndrome occurrence than such inflammatory state parameters as hs-CRP and IL-6 [21]. Hence adiponectin may become a routine laboratory measurement for estimating the risk factor for the occurrence of metabolic syndrome [25, 26].

The concentrations of pro-inflammatory adipokines and cytokines such as resistin, leptin, and TNF-$\alpha$ were similar in MS and nonMS group. IL-6 was the only one that was higher in the group with metabolic syndrome. Other authors [18, 23] have also failed to show any differences in leptin and resistin concentrations between patients with and without metabolic syndrome.

The results concerning levels of TNF-$\alpha$ are divergent. Similarly to our study, You and others did not observe any difference in TNF-$\alpha$ between patients with and without metabolic syndrome [19]. Others described higher concentrations of this cytokine in patients with metabolic syndrome but only when ATP III criteria are taken into consideration (not according to IDF) [18, 21, 27].

In our study, hs-CRP did not differ but only showed a tendency towards higher concentration in the group with metabolic syndrome. It is in agreement with observations made by other authors who did not describe any difference in hs-CRP concentrations between obese people with and without metabolic syndrome [18, 19]. Nevertheless, higher concentrations of hs-CRP were even described in teenagers with metabolic syndrome. Hs-CRP value > 3 mg/L was noted 3.5 times more often in patients with metabolic syndrome than in those without [28]. It is worth mentioning that in multivariate regression analysis, waist circumference was the only component of metabolic syndrome that had a significant influence on hs-CRP.

Komatsu and others [24] suggest that the increase of hs-CRP concentration is a later phenomenon than

the decrease in adiponectin concentration; thus, hs-CRP concentration may be normal at the beginning of metabolic syndrome occurrence. This may explain the results observed by us.

In our study, plasma concentrations of adiponectin were significantly higher in the MS group (Table III), in comparison to the nonMS group. However, adiponectin levels became lower along with an increase in insulin resistance and obesity. Some authors have confirmed such a correlation [29–35]. Altinova and others [36] suggested, on the basis of multivariate analysis, that adiponectin concentration has a decisive influence on insulin resistance level.

In the studied group, decreased concentrations of adiponectin co-existed with low HDL cholesterol and increased triglycerides. No correlation has been found between adiponectin and total cholesterol and LDL fraction. In addition, we observed a negative correlation between adiponectin and SBP and DBP. Thus, along with the decrease in adiponectin concentration, lipid disturbances and hypertension are observed — typical for metabolic syndrome. These results suggest a relation between hypoadiponectinaemia and increased metabolic complications [33, 37, 38].

## Summary

Incidence rates of metabolic syndrome increase with obesity intensification; however, it is not present in all obese persons. Apart from obesity rate, genetic predispositions also have an influence on metabolic syndrome manifestation. It seems to be useful to isolate subjects with high risk of complications in the population of obese patients. One such a marker can be adiponectin, the level of which correlates with the presence of cardiovascular complications. Identification of low adiponectin level obese patients could offer them particular care due to enhanced mortality risk.

## Conclusions

1. In obese people, a low concentration of adiponectin correlates with disturbances typical for metabolic syndrome. Therefore, hypoadiponectinaemia can be a factor influencing the development of the metabolic disorders.
2. Adiponectin concentration could be a marker of high risk of cardiovascular diseases in obese patients with, and without, metabolic syndrome.

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