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Original Article

Is HS-CRP useful in identifying a subset of normal-weight women with higher cardiovascular risk?

Vahideh Aghamohammadi [1], Meysam Alipour [2] *, Damoon Ashtary-Larky [3], Hadi Bazyar [4], Neda Haghighat [5], Khadijeh Nasiri [1], Amir Abbasnezhad [6]

[1] Department of Nutrition, Khalkhal University of Medical Sciences, Khalkahl, Iran
[2] Department of Nutrition, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran
[3] Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4] Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[5] Laparoscopy Research Center, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[6] Department of Nutrition, Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

* Correspondence to: Meysam Alipour, Department of Nutrition, Shoushtar Faculty of Medical Sciences, Shoushtar, Iran. Phone: +98 6136224243; Fax: +98 613626185; E-mail: meysam.aalipour@yahoo.com

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Abstract

Due to the paucity of information on high-sensitivity C-Reactive Protein (hs-CRP) identifying an at-risk group of non-obese individuals with a higher risk of subclinical atherosclerosis, we decided to evaluate hs-CRP identifying cardiovascular risks on inflammatory obesity phenotypes. We studied 154 women aged 20–35 years. Inflammatory status was defined as a serum hs-CRP level ≥2 mg/L. Individuals were grouped according to inflammatory obesity phenotypes: 1) IHNW: inflammatory healthy normal weight, 2) IUNW: inflammatory unhealthy normal weight, 3) IHO: inflammatory healthy obese, 4) IUO: inflammatory unhealthy obese. Body composition was significantly better in the IHO group compared to the IUO group($P<0.001$), except for lean body mass in the left and right leg. After adjustment for covariates, the IHNW and IUNW had significant differences in hs-CRP, FBS and lipid profile($P<0.05$). The IUO phenotype individuals had significantly more Cho/HDL, LDL/HDL and Atherogenic Index of Plasma($P<0.05$). Moreover, the HOMA-s percentage was significantly higher in the IHO group compared to the IUO group. In conclusion, hsCRP ≥2 mg/L is useful in identifying a subset of obese and non-obese women with higher CVD risk. High hs-CRP, in the absence of obesity, could distinguish non-obese subset subjects with cardiovascular risk.

Keywords: cardiovascular disease, C-Reactive Protein, obesity.

Introduction

Obesity is one of the major nutritional disorders in developed countries and is supposed to become a health problem in developing countries, including Iran. As stated by the latest World Health Organization report, more than half of Iranian adults are overweight or obese [1, 2]. These disorders are substantial risk factors in the development of type 2 diabetes, hypertension, atherosclerosis, cancers, acute pancreatitis, fatty liver diseases, and rheumatoid arthritis disease [3–6]. Obesity can be a hypothesis as low-grade and chronic inflammation [7]. The inflammatory response elicited by obesity characterized by insulin resistance increased blood concentrations of C-reactive protein, IL-6, IL-8, TNF-α, and other cytokines.8 In all phases of atherosclerosis, from the recruitment of circulating leukocytes to the arterial wall, inflammation has primary roles. Hs-CRP is an accessible and nonspecific biomarker and can be measured inexpensively with convenient

high-sensitivity tests [8, 9]. By contrasting other markers of inflammation, its levels are stable over a long time and have no daily fluctuation. It is mostly made in the liver in response to IL-6, which is one of the main cytokines released by activated leukocytes and smooth muscle cells in atherosclerotic plaques [10]. The presence or absence of Inflammation is assessed by hs-CRP, which could be useful in recognizing a subset of obese individuals without an increased atherosclerotic burden or a subset of non-obese individuals with a higher atherosclerosis burden compared to their non-inflammatory counterparts [11]. A certain amount of knowledge is required to determine the extent of a disease's relationship with CPR levels independent of common risk factors [10].

Since not all obese individuals show an increased risk of inflammation, and not all normal-weight individuals are metabolically healthy or free from cardiovascular disease, more studies are needed to clarify the cardiovascular risks in these individuals. Besides, due to the paucity of information on the potential role of hs-CRP in identifying an at-risk group of non-obese individuals with a higher prevalence of subclinical atherosclerosis and obese subjects without an increase in cardiovascular risks, we decided to assess whether hs-CRP could identify cardiovascular risks in four inflammation obesity phenotypes in Iranian women.

Material and methods

Participants

We studied 154 women aged 20–35 years from a population of 308 volunteers who were referred to a nutrition clinic in Ahvaz, Iran. We excluded 154 participants who met exclusion criteria (including pregnancy, breastfeeding, consumption of any drugs, diabetes, cardiovascular disease, kidney disorders, thyroid, digestive and respiratory diseases, and cancer, consuming more than 300 mg of caffeine daily, who had moderate or various physical activities). Inclusion criteria were having regular 28-d menstrual cycles, no smoking, alcohol, and consumption of any supplements, and lack of weight changes in the last six months. Inflammation was defined as a serum hs-CRP level ≥2 mg/L, per criteria used in the JUPITER statin trial [12]. Then, we identified four phenotypes (Table 1). All subjects gave written informed consent, and the ethical committee of Ahvaz Jundishapur University of Medical Sciences approved the protocol (Approval number: IR.AJUMS.REC.1394.489).

Measurements

Waist circumference (WC) was measured in a standing position using a tape with an accuracy of 1.0 cm above the iliac crest, just below the lowest rib margin at the end of the regular expiration; for hip circumference measurement, the tape was placed around the point with the maximum circumference over the buttocks [13]. The waist-hip ratio or waist-to-hip ratio (WHR) is the dimensionless ratio of the circumference of the waist to that of the hips. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were computed using an automatic blood pressure monitor (BM65, Beurer, Germany) after subjects rested for more than 10 minutes. The measurements were done in triplicates, and the mean was considered for each subject. DSM-BIA (Inbody 270, Biospace, Korea) was used to calculate body composition, including lean body mass (LBM), fat mass (FM), total body water (TBW), fat-free mass (FFM), body mass index (BMI), body fat percentage (BFP). RMR (Resting Metabolic rate) was quantified using resting oxygen uptake (VO_2). Fasting blood glucose (FBS) and lipid profile were measured by the enzymatic method. ELISA kits determined insulin and hs-CRP concentrations. The following formula calculated the insulin resistance (HOMA-IR): fasting glucose (mg/dl) × fasting insulin (μu/ml)/405 [14]. The atherogenic index

Table 1: The criteria used in the diagnosis of the inflammatory obese phenotypes.

Inflammatory obese phenotypes	BMI	hsCRP
IHNW – inflammatory healthy normal weight	<25 (kg/m²)	<2 mg/L 1
IUNW – inflammatory unhealthy normal weight	<25 (kg/m²)	≥2 mg/L
IHO – inflammatory healthy obese	≥25 (kg/m²)	<2 mg/L
IUO – inflammatory unhealthy obese	≥25 (kg/m²)	≥2 mg/L

Note: BMI – body mass index; hs-CRP – high sensitivity C-reactive protein.

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of plasma (AIP) was calculated as the logarithm of the molar ratio of TG/HDL-C.

Statistical analyses

All statistical analyses were performed by using IBM SPSS Statistics software version 24. ANOVA (post-hoc; Tukey) was used to assay differences within groups. Analysis of covariance (ANCOVA) test was used to control confounding variables. Stepwise linear regression was applied to assess hsCRP associations with anthropometric and biochemistry factors. P<0.05 was considered a significant difference.

Results

The number of participants in the four inflammatory phenotypes and their characteristics are shown in Table 2. The mean age of the total population was 27.34±4.69. In terms of age, groups had no significant difference. Approximately 45% had high hs-CRP. We observed 28% of non-obese individuals with significant inflammation by hs-CRP ≥2 mg/L criteria, while 30% of obese subjects did not have significant inflammation. Among the 4 study groups, there were not significant differences in weight, HR, and DBP (P>0.05). The IHNW and IUNW groups did not have significant differences in RMR, SBP, HC, WC, BFP, WHR, LBM, FFM, FM, and TBW variables. Compared to the IHO group, the IUO group had significantly more RMR, HC, WC, BFP, WHR, LBM, FFM, FM, and TBW(P<0.05), but these two groups were similar in SBP, DBP, and HR(P>0.05). As shown in Table 3, except for LBM left and right leg, other body composition variables in the IUO group were significantly higher than in the IHO group(P>0.05). According to Table 4, after adjustment for covariates, the IHNW and IUNW had significant differences in the blood concentration of FBS, Cho, TG, HDL-c, LDL-c, and Cho/HDL(P>0.05). The results of ANCOVA showed that the IUO phenotype individuals had significantly more Cho/HDL, HDL/LDL, ALP, and AIP and significantly less HDL-C compared to the IHO group, which is some characteristic of rising metabolic syndrome prevalence.

In the overall population, multiple stepwise linear regression analysis using serum hs-CRP as a dependent variable and all other biochemical parameters as independent variables indicated that LDL/HDL ratio (β=0.316, P<0.001) and FBS (β=0.238, P=0.002) were independently associated with serum hs-CRP.

Discussion

We observed in the absence of obesity, hs-CRP <2 mg/L identified a subset of women with a lower risk of atherosclerosis. Also, among obese women, hsCRP ≥2 mg/L discriminates the subset of them with at-risk atherosclerosis. Also, a strong correlation between obesity and hs-CRP was established. Little information is available on the usefulness of current cardiovascular risk prediction tools in obese subjects, although the growth in the prevalence of obesity is speedy [8]. Due to the population of most studies regarding the utility of CRP or hs-CRP, they consist of white individuals. Thus, few data are available in other races [15–18]. We used the JUPITER and Lin *et al*. study cutoff of hs-CRP ≥2 mg/L to categorize high and low inflammation subsets [11, 12]. In line with our findings, results from two other studies showed that a high hs-CRP value was usable in distinguishing an at-risk group of non-obese participants with a higher prevalence of subclinical atherosclerosis, but the authors did not demonstrate a significant gender effect in their results [11, 19]. Lin *et al*. found gender differences in the association of inflammation with atherosclerosis, hs-CRP ≥2 mg/L was related to elevated carotid intima–media thickness in non-obese men but not in women.11 The authors stated that the absence of association between hs-CRP and atherosclerosis in women links up to physiologically higher hs-CRP levels observed in women; it is possible that estrogen-induced changes in hs-CRP are not associated with the progression of atherosclerosis [20–22]. Virendra *et al*. concluded that hs-CRP could be regarded as a novel coronary artery disease (CAD) risk factor to be screened in patients with CAD where traditional risk factors cannot predict it. Half of the CADs belong to common risk factors; the rest are unexplained [23]. Moreover, in the study by Carrero *et al*., most patients (>60%) with myocardial infarction had hs-CRP ≥2 mg/L. The authors demonstrated hs-CRP's commonness and prognostic significance for the risk of death and major adverse cardiovascular events in secondary prevention [24]. It is worth mentioning that our participants were younger non-menopause women compared to other studies and were Iranian (different racial). Indeed, because of obesity's interconnection with several other emerging atherosclerotic risk factors containing prediabetes, atherogenic dyslipidemia, decreased adiponectin, leptin resistance, decreased plasminogen activator inhibitor-1, and microalbuminuria, the vascular biology of obesity is complex [25]. Further studies are needed to illuminate the association between hs-CRP and

Table 2: Anthropometric status between groups.

Variables	Total population (n=154)	IHNW (n=41)	IUNW (n=16)	IHO (n=29)	IUO (n=68)	PV
Age (years)	27.34±4.69	26.07±5.12	27.69±4.64	28.38±4.20	27.57±4.58	0.19
Weight (kg)	77.06±19.87	56.72±6.16[b, c]	57.81±6.04[d, e]	80.30±12.15[f]	92.46±14.92	<0.001
Height (cm)	159.18±5.21	159.42±5.23	159.00±5.70	160.42±4.63	158.55±5.33	0.44
Lean body mass (kg)	24.37±4.41	21.57±2.53[b, c]	20.22±2.29[d, e]	24.71±3.37[f]	26.90±4.39	<0.001
Fat mass (kg)	32.86±14.47	17.25±4.95[b, c]	20.14±3.75[d, e]	35.24±7.59[f]	44.25±10.70	<0.001
Total body water (kg)	32.40±4.85	28.91±2.64[b, c]	27.56±2.86[d, e]	32.93±4.13[f]	35.42±4.26	<0.001
Fat-free mass (kg)	43.96±6.26	39.42±3.59[b, c]	37.63±3.90[d, e]	45.00±5.62	47.75±5.30	<0.001
Body mass index (kg/m²)	30.52±8.02	22.32±2.36[b, c]	22.82±1.61[d, e]	31.19±4.10[f]	36.99±6.16	<0.001
Percentage of body fat (%)	40.76±9.02	30.00±6.21[a, b, c]	34.68±4.38[d, e]	43.56±3.88[f]	47.50±4.82	<0.001
Waist hip ratio	0.83±0.08	0.76±0.05[b, c]	0.76±0.06[d, e]	0.83±0.06[f]	0.88±0.06	<0.001
Waist circumference (cm)	89.20±16.63	70.75±5.61[b, c]	74.00±5.48[d, e]	92.70±9.49[f]	102.40±11.08	<0.001
Hip circumference (cm)	106.33±12.34	92.51±5.14[b, c]	95.87±4.59[d, e]	110.10±7.79[f]	115.52±8.18	<0.001
Heart rate (n)	91.92±12.94	93.97±14.72	93.87±11.49	89.13±11.19	91.42±12.81	0.42
Systolic blood pressure (mmHg)	118.79±14.76	113.81±12.76[b, c]	112.47±8.39[d]	123.74±15.44	121.17±15.62	0.005
Diastolic blood pressure (mmHg)	77.29±13.40	76.11±10.41	75.53±8.79	75.80±20.37	75.05±12.21	0.55
Resting metabolic rate	1456.74±149.48	1345.62±85.39[b, c]	1302.40±92.89[d, e]	1478.03±133.64[f]	1550.97±121.76	<0.001

Note: IHNW – inflammatory healthy normal weight; IUNW – inflammatory unhealthy normal weight; IHO – inflammatory healthy obese; IUO – inflammatory unhealthy obese; [a] – significant difference between IHNW compare to IUNW; [b] – significant difference between IHNW compare to IHO; [c] – significant difference between IHNW compare to IUO; [d] – significant difference between IUNW compare to IHO; [e] – significant difference between IUNW compare to IUO; [f] – significant difference between IHO compare to IUO.

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Table 3: Body composition between groups.

Variables	Total population (n=154)	IHNW (n=41)	IUNW (n=16)	IHO (n=29)	IUO (n=68)	PV
LBM_left_arm (kg)	2.30±0.52	1.85±0.28 [b, c]	1.76±0.26 [d, e]	2.38±0.43 [f]	2.66±0.38	<0.001
LBM_right_arm (kg)	2.31±0.51	1.88±0.28 [b, c]	1.80±0.30 [d, e]	2.40±0.42 [f]	2.66±0.38	<0.001
LBM_trunk (kg)	20.18±3.14	17.48±1.76 [b, c]	17.09±1.91 [d, e]	20.78±2.63 [f]	22.28±2.35	<0.001
LBM_left_leg (kg)	6.60±1.02	5.96±0.73 [b, c]	5.67±0.71 [d, e]	6.72±0.86	7.16±0.92	<0.001
LBM_right_leg (kg)	6.64±1.04	5.97±0.73 [b, c]	5.68±0.72 [d, e]	6.73±0.86	7.22±0.93	<0.001
FM_left_arm (kg)	3.02±1.89	1.19±0.44 [b, c]	1.43±0.33 [d, e]	3.08±0.99 [f]	4.48±1.68	<0.001
BFP_left_arm (%)	50.84±12.20	37.06±8.77 [a, b, c]	43.15±6.40 [d, e]	54.04±5.27 [f]	59.60±7.79	<0.001
FM_right_arm (kg)	2.99±1.89	1.16±0.42 [b, c]	1.41±0.33 [d, e]	3.05±1.01 [f]	4.45±1.67	<0.001
BFP_right_arm (%)	50.28±12.50	36.01±8.46 [a, b, c]	42.39±6.80 [d, e]	53.46±5.62 [f]	59.39±7.92	<0.001
FM_tunk (kg)	15.90±6.50	8.49±2.69 [b, c]	10.10±2.08 [d, e]	17.57±3.62 [f]	21.02±4.02	<0.001
BFP_trunk (%)	40.83±8.26	30.78±6.57 [a, b, c]	35.56±4.38 [d, e]	44.03±3.17 [f]	46.77±3.58	<0.001
FM_left_leg (kg)	4.83±2.09	2.68±0.69 [b, c]	3.06±0.54 [d, e]	5.06±0.95 [f]	6.46±1.73	<0.001
BFP_left_leg (%)	39.16±8.46	29.54±5.90 [a, b, c]	33.60±4.11 [d, e]	41.29±3.68 [f]	45.35±5.33	<0.001
FM_right_leg (kg)	4.87±2.12	2.70±0.68 [b, c]	3.06±0.55 [d, e]	5.09±0.96 [f]	6.51±1.77	<0.001
BFP _right_leg (%)	39.18±8.42	29.66±5.77 [b, c]	33.55±4.13 [d, e]	41.36±3.75 [f]	45.32±5.38	<0.001
LBM (%)	32.58±5.00	38.18±3.71 [a, b, c]	35.03±2.51 [d, e]	30.90±2.06	29.34±3.65	<0.001
FM/LBM	1.31±0.45	0.80±0.24 [b, c]	1.00±0.18 [d, e]	1.42±0.22 [f]	1.64±0.31	<0.001
left_arm_FM/LBM	1.23±0.57	0.66±0.27 [b, c]	0.82±0.20 [d, e]	1.28±0.27 [f]	1.65±0.50	<0.001
right_arm_FM/LBM	1.21±0.58	0.63±0.25 [b, c]	0.80±0.21 [d, e]	1.25±0.27 [f]	1.64±0.51	<0.001
trunk_FM/LBM	0.76±0.23	0.48±0.15 [a, b, c]	0.59±0.10 [d, e]	0.84±0.11 [f]	0.93±0.12	<0.001
left_leg_FM/LBM	0.72±0.24	0.45±0.13 [b, c]	0.54±0.09 [d, e]	0.75±0.11 [f]	0.89±0.18	<0.001
right_leg_FM/LBM	0.72±0.24	0.46±0.13 [b, c]	0.54±0.09 [d, e]	0.76±0.11 [f]	0.89±0.19	<0.001

Note: IHNW – inflammatory healthy normal weight; IUNW – inflammatory unhealthy normal weight; IHO – inflammatory healthy obese; IUO – inflammatory unhealthy obese; LBM – lean body mass; FM – fat mass; BFP – body fat percentage; [a] – significant difference between IHNW and IUNW; [b] – significant difference between IHNW and IHO; [c] – significant difference between IHNW and IUO; [d] – significant difference between IUNW and IHO; [e] – significant difference between IUNW and IUO; [f] – significant difference between IHO and IUO.

Table 4: Comparison of mean of biochemistry variables between groups.

Variables	Total population (n=154)	IHNW (n=41)	IUNW (n=16)	IHO (n=29)	IUO (n=68)	P1	P2
Fasting blood sugar (mg/dl)	89.49±10.14	84.92±8.64 [a, c, g, i]	92.18±8.88	88.72±9.22 [f]	91.94±10.78	0.003	0.003
Cholesterol (mg/dl)	180.42±30.67	167.56±21.99 [b, c, g]	187.68±27.90 [k]	186.51±33.81	183.88±32.65	0.016	0.026
Triglyceride (mg/dl)	116.96±50.55	93.34±45.99 [c, g]	112.37±54.34	119.93±49.29	131.01±48.43	0.002	0.121
High-density lipoprotein(mg/dl)	46.44±9.68	52.85±7.14 [c, g]	49.93±7.69 [e, k]	48.48±9.36 [f, l]	40.88±8.52	<0.001	<0.001
Low-density lipoprotein (mg/dl)	111.45±29.80	95.09±18.56 [a, b, c, g, h, i]	115.31±29.62	114.79±30.80	118.98±31.62	<0.001	0.001
LDL/HDL	2.58±1.07	1.85±0.51 [b, c, i]	2.44±1.10 [k]	2.52±0.85 [l]	3.07±1.14	<0.001	<0.001
Cholesterol/HDL	4.12±1.30	3.28±0.90 [b, c, g]	3.91±1.25 [k]	4.07±1.07 [l]	4.70±1.33	<0.001	0.001
TG/LDL	1.09±0.53	1.02±0.60 [i]	1.03±0.57	1.11±0.54	1.15±0.47	0.64	0.560
VLDL (mg/dl)	23.39±10.11	18.66±9.19 [c, i]	22.47±10.86	23.98±9.85 [f]	26.21±9.68	0.002	0.060
Aspartate transaminase	23.90±13.76	21.68±7.77 [g]	29.50±31.38	20.79±7.15	25.25±11.76	0.12	0.720
Alanine transaminase	22.60±11.56	18.80±8.17 [c, i]	22.37±15.84	20.96±8.67	25.64±12.59	0.02	0.019
Alkaline phosphatase	186.41±55.99	178.51±42.05	186.81±47.22	165.66±62.99 [f, l]	199.94±59.46	0.03	0.043
Insulin	11.13±6.59	9.86±6.10 [i]	10.73±4.62	10.30±6.57	12.35±7.17	0.22	0.820
Insulin resistance (HOMA-IR)	1.42±0.82	1.24±0.73 [i]	1.39±0.59	1.31±0.82	1.58±0.90	0.17	0.625
HOMA_S_percentage	91.29±45.66	101.74±47.01 [i]	85.78±37.90	103.10±56.19 [l]	81.26±39.55	0.05	0.021
HOMA_B_percentage	123.80±52.45	127.33±59.48 [h]	114.38±38.96	117.88±52.83 [i]	126.42±51.11	0.75	0.670
hs-CRP	3.95±4.80	0.95±0.55 [c, g]	3.10±1.09 [e, j, k]	0.82±0.51 [f, l]	7.29±5.56	<0.001	<0.001
Atherogenic Index of Plasma	0.73±0.23	0.58±0.17 [b, c, h, i]	0.67±0.23 [e, k]	0.72±0.21 [f, l]	0.84±0.21	<0.001	<0.001

IHNW – inflammatory healthy normal weight; IUNW – inflammatory unhealthy normal weight; IHO – inflammatory healthy obese; IUO – inflammatory unhealthy obese; P1 – ANOVA; P2 – Analysis of covariance (adjusted for age, LDL-c, SBP and DBP); [a] – significant difference between IHNW and IUNW; [b] – significant difference between IHNW and IHO; [c] – significant difference between IHNW and IUO; [d] – significant difference between IUNW and IHO; [e] – significant difference between IUNW and IUO; [f] – significant difference between IHO and IUO; [g] – adjusted significant difference between IHNW and IUNW; [h] – adjusted significant difference between IHNW and IHO; [i] – adjusted significant difference between IHNW and IUO; [j] – adjusted significant difference between IUNW and IHO; [k] – adjusted significant difference between IUNW and IUO; [l] – adjusted significant difference between IHO and IUO.

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cardiovascular events across gender-specific obesity phenotypes in Iranians. Further investigations are suggested to determine the role of CRP in non-atherosclerotic pathways such as thrombosis, decreased fibrinolysis, and plaque frailty [26]. The present study has a cross-sectional nature, and this is one of the limitations, so we couldn't establish a causality relationship. Due to funding complications, we did not measure the angiographic atherosclerosis burden. Our population indeed had one race; although the multi-ethnic compound of studies increases generalizability, it can limit the precise characterization of obesity in different ethnicities.

Conclusion

Hs-CRP ≥2 mg/L was useful in identifying a subset of obese and non-obese women with higher CVD risk. High hs-CRP, in the absence of obesity, could distinguish non-obese subset subjects with cardiovascular risk.

Conflict of interest

The authors declare no conflict of interest.

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