

Abdominal Adiposity Is a Stronger Predictor of Insulin Resistance Than Fitness Among 50–95 Year Olds

SUSAN B. RACETTE, PHD¹
ELLEN M. EVANS, PHD¹
EDWARD P. WEISS, PHD^{1,2}

JAMES M. HAGBERG, PHD²
JOHN O. HOLLOSZY, MD¹

OBJECTIVE — Physical inactivity and increased adiposity contribute to insulin resistance; less is known, however, about the relative contributions of these factors in older adults. The aim of this study was to determine whether cardiovascular fitness, whole-body adiposity, or abdominal adiposity is the strongest predictor of insulin resistance into old age.

RESEARCH DESIGN AND METHODS — Subjects included 407 men and women aged 50–95 years (means \pm SD 69 \pm 11 years). Insulin resistance was estimated using the insulin sensitivity index (ISI) of Matsuda and DeFronzo [ISI = 10,000/square root of (fasting glucose \times fasting insulin) \times (mean glucose \times mean insulin during an oral glucose tolerance test)]; lower ISI = greater insulin resistance]. Fitness was determined with a treadmill maximal oxygen consumption (VO_{2max}) test. Whole-body adiposity measures included BMI and percent fat by dual-energy X-ray absorptiometry or hydrodensitometry; abdominal adiposity was estimated by waist circumference.

RESULTS — Waist circumference was the strongest independent correlate of ISI ($r = -0.52$, $P < 0.0001$), explaining 28% of the variance when controlling for sex, BMI, percent fat, and VO_{2max} . BMI ($r = -0.45$), percent fat ($r = -0.40$), and VO_{2max} ($r = 0.22$) independently predicted ISI (all $P < 0.0001$); however, after controlling for waist circumference, only VO_{2max} remained significant ($r = 0.13$, $P = 0.009$).

CONCLUSIONS — Adiposity and fitness continue to be significant predictors of insulin sensitivity into old age, with abdominal obesity being the most important single factor. These findings support the measurement of waist circumference to assess health risk among older adults.

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Ageing generally is associated with reduced aerobic capacity (1,2) and increases in abdominal adiposity and insulin resistance (3). The decline in maximal aerobic power is attributable largely to age-associated reductions in cardiac and skeletal muscle cell mass and function, as well as to declines in vital capacity. However, a physically inactive lifestyle also plays an important role. The cardiovascular system maintains its capacity to adapt to exercise stimuli into old

age (4,5), and prospective studies have shown that habitual physical activity enhances insulin action and protects against insulin resistance that leads to type 2 diabetes (6,7). Among young and middle-aged adults, both poor fitness due to a sedentary lifestyle and abdominal obesity contribute to insulin resistance. The relationship between fitness, whole-body adiposity, abdominal adiposity, and insulin resistance, however, is largely unknown among the elderly.

Age-associated alterations in body composition include reductions in lean body mass (8) and increases in adiposity (9), due in part to hormonal changes associated with menopause in women and adrenopause in men, as well as decrements in physical activity. There has been a great deal of interest in exploring the relative importance of fitness and fatness to health and disease risk factors. The two recommended measurements for assessing weight-related health risk are BMI, which has gained international acceptance because of its associations with adiposity, disease risk (10), and mortality (11), and waist circumference, which is associated with visceral adipose tissue (12,13), the metabolic syndrome (14), insulin resistance (15), and type 2 diabetes (16). BMI, however, may not accurately reflect health risk among older adults who may have a BMI value in the healthy range despite muscle loss and excess abdominal fat. Waist circumference and body composition assessments are likely to provide more valuable information regarding health risk among the elderly.

Although obesity and abdominal obesity are well-known health risk factors, the contribution of these factors to insulin resistance among older adults has not been studied extensively. Therefore, the primary aim of the current study was to examine the relative contributions of cardiovascular fitness, whole-body fatness, and abdominal adiposity to insulin resistance among men and women ranging in age from 50 to 95 years.

RESEARCH DESIGN AND METHODS

Healthy men and women between 50 and 95 years of age who were enrolled in one of six clinical studies in the Applied Physiology Laboratory at Washington University School of Medicine or the Exercise Physiology Laboratory at the University of Maryland and who completed measurements of maximal oxygen consumption (VO_{2max}), body composition, BMI, waist circumference, and an oral glucose tolerance test (OGTT) were eligible for this analysis. All subjects were ambulatory, weight stable for at least

From the ¹Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; and the ²Department of Kinesiology, University of Maryland, College Park, Maryland.

Address correspondence and reprint requests to Susan B. Racette, PhD, Washington University School of Medicine, Campus Box 8502, 4444 Forest Park Ave., St. Louis, MO 63108-2212. E-mail: racettes@wustl.edu.

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Abbreviations: AUC, area under the curve; ISI, insulin sensitivity index; NHANES, National Health and Nutrition Examination Survey; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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3 months before enrollment, and non-smokers. Although subjects had varying levels of habitual physical activity, none were engaged in an exercise training program for >2 days/week. All studies were approved by the Washington University School of Medicine Human Studies Committee and the General Clinical Research Center Scientific Advisory Committee or by the University of Maryland Institutional Review Board. Written, informed consent was obtained from each participant.

Anthropometry and body composition

Height was measured without shoes to the nearest 0.1 cm. Body weight was obtained on a balance scale in the morning after a 12-h fast. BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured at the midpoint between the iliac crest and the bottom of the rib cage using a spring-loaded measuring tape. Total body fat mass and fat-free mass were assessed by either dual-energy X-ray absorptiometry (Hologic, Waltham, MA, or DPX-L; Lunar, Madison WI; $n = 273$) or hydrodensitometry ($n = 134$).

OGTT

In the morning after a 10- to 12-h fast, 75-g, 2-h OGTTs were conducted. Subjects taking oral hypoglycemic agents withheld their medications 24 h before the OGTT, and none were treated with insulin. Blood samples were drawn for the determination of plasma glucose and insulin concentrations before and every 30 min after administration of the glucose beverage. Glucose was measured by the glucose oxidase method and insulin by radioimmunoassay. Total areas under the curve (AUCs) for glucose and insulin were calculated using the trapezoidal rule. The insulin sensitivity index (ISI) of Matsuda and DeFronzo (17) was calculated as: $10,000/\text{square root of (fasting glucose} \times \text{fasting insulin)} \times (\text{mean OGTT glucose} \times \text{mean OGTT insulin})$. The primary outcome of interest was insulin resistance, which was estimated by the ISI, with lower ISI values indicating a greater degree of insulin resistance.

$\text{VO}_{2\text{max}}$

A graded treadmill exercise test was conducted to determine maximal oxygen uptake capacity as an indicator of cardiovascular fitness. Following a 5-min warm up with 0% grade, subjects walked at a

Table 1—Subject characteristics

	Women	Men	All
<i>n</i>	290	117	407
Age (years)	69 ± 11	69 ± 12	69 ± 11
Height (cm)	161.0 ± 6.6	175.3 ± 7.2*	165.1 ± 9.3
Weight (kg)	69.4 ± 12.5	82.8 ± 12.5*	73.3 ± 13.9
BMI (kg/m ²)	26.8 ± 4.4	26.9 ± 3.5	26.8 ± 4.2
Fat mass (%)	39.8 ± 6.9	28.2 ± 5.6*	36.4 ± 8.4
Fat mass (kg)	27.7 ± 8.7	23.3 ± 7.1*	26.4 ± 8.5
Fat-free mass (kg)	40.6 ± 5.1	57.9 ± 7.0*	45.6 ± 9.7
Waist circumference (cm)	85.1 ± 10.5	96.4 ± 9.8*	88.3 ± 11.5
$\text{VO}_{2\text{max}}$ (ml · kg ⁻¹ · min ⁻¹)	19.5 ± 4.7	23.4 ± 6.6*	20.6 ± 5.6
$\text{VO}_{2\text{max}}$ (l/min)	1.35 ± 0.40	1.94 ± 0.61*	1.52 ± 0.54
Fasting plasma glucose (mmol/l)	5.2 ± 0.6	5.4 ± 0.6†	5.2 ± 0.6
Fasting plasma insulin (pmol/l)	58.8 ± 48.6	64.6 ± 40.9‡	60.5 ± 46.5
ISI	5.32 ± 3.14	4.43 ± 2.41†	5.06 ± 2.97
Glucose AUC (mmol · l ⁻¹ · min ⁻¹)	959 ± 214	1,008 ± 204‡	973 ± 212
Insulin AUC (×10 ³ , pmol · l ⁻¹ · min ⁻¹)	41.3 ± 20.4	47.7 ± 25.0‡	43.2 ± 22.0

Data are means ± SD. * $P < 0.0001$, † $P < 0.01$, ‡ $P < 0.05$ for difference between women and men.

pace that elicited 60–70% of age-predicted maximal heart rate ($220 - \text{age}$), and the grade was increased 1–2% every 1–2 min until the subject was unable to continue because of volitional exhaustion, electrocardiographic changes, or another physiologic response that rendered it unsafe to continue. VO_2 was measured continuously using open-circuit spirometry (5). $\text{VO}_{2\text{max}}$ was calculated as the mean of the two highest consecutive 30-s VO_2 values that met ≥ 2 of the following criteria: 1) plateau in VO_2 despite increasing exercise intensity; 2) maximal heart rate within 10 bpm of age-predicted maximum; and 3) respiratory exchange ratio > 1.10 .

Statistical analyses

Analyses were performed using SPSS statistical software (version 12.0.1; Chicago, IL). Distribution statistics for the residuals were calculated to determine whether assumptions of normality were met (i.e., skewness and kurtosis < 2.0). The residuals for ISI, fasting glucose and insulin, and glucose and insulin AUC were skewed. Therefore, these data were log transformed for statistical analyses; the raw data are presented in the text and tables for more meaningful comparisons. Student's *t* tests were used to assess sex differences in subject characteristics. Correlation coefficients and stepwise multiple linear regression analyses were used to determine the relationships between measures of insulin resistance (i.e., ISI as primary outcome, insulin AUC, and glucose AUC as secondary outcomes) and

measures of adiposity (i.e., BMI, percent fat, and waist circumference) and cardiovascular fitness. Sex was controlled for in all analyses because of the physiological differences in $\text{VO}_{2\text{max}}$, percent fat, and waist circumference between women and men. All data in the text and tables are represented as means ± SD. Significance was accepted at an α level of 0.05.

RESULTS

Four hundred seven adults (290 women and 117 men) met the criteria for inclusion in these analyses. Although race was not recorded for 134 subjects, the remaining sample was 82% white, 15% black, and 3% of other racial background. The percentages of participants classified as having normal glucose tolerance, pre-diabetes, or diabetes (18) were 55, 34, and 11%, respectively. Although many of the older adults were taking a variety of medications (e.g., aspirin or antihypertensive medications), all subjects were ambulatory and were eligible to participate in an exercise training study. The characteristics for all subjects, for women, and for men are shown in Table 1. The men in our sample were more insulin resistant (reflected by lower ISI and higher insulin AUC) and had poorer glucose tolerance than the women.

Predictors of insulin resistance

The three measures of adiposity (BMI, percent fat, and waist circumference) were highly correlated with each other ($r = 0.66-0.84$; all $P < 0.001$). Waist circumference, an estimate of abdominal adiposity, was the strongest independent

Table 2—Correlation coefficients for the associations between measures of insulin resistance, adiposity, and fitness

Controlling for*	ISI		Insulin AUC		Glucose AUC	
	r	P	r	P	r	P
Waist	-0.52	<0.0001	0.43	<0.0001	0.24	<0.0001
BMI	-0.29	<0.0001	0.26	<0.0001	0.22	<0.0001
% fat	-0.38	<0.0001	0.33	<0.0001	0.21	<0.0001
VO _{2max}	-0.50	<0.0001	0.41	<0.0001	0.19	<0.0001
BMI, % fat, VO _{2max}	-0.27	<0.0001	0.25	<0.0001	0.20	<0.0001
BMI	-0.45	<0.0001	0.36	<0.0001	0.15	0.002
Waist	-0.03	0.585	-0.01	0.867	-0.10	0.037
% fat	-0.26	<0.0001	0.23	<0.0001	0.08	0.089
VO _{2max}	-0.43	<0.0001	0.34	<0.0001	0.10	0.053
% fat, waist, VO _{2max}	-0.00	0.933	-0.01	0.791	-0.09	0.063
% fat	-0.40	<0.0001	0.29	<0.0001	0.13	0.009
Waist	-0.08	0.093	0.01	0.776	-0.04	0.412
BMI	-0.11	0.021	0.05	0.285	0.03	0.536
VO _{2max}	-0.37	<0.0001	0.27	<0.0001	0.06	0.215
BMI, waist, VO _{2max}	-0.07	0.187	-0.01	0.858	-0.04	0.484
VO _{2max}	0.22	<0.0001	-0.17	0.001	-0.34	<0.0001
Waist	0.13	0.009	-0.09	0.063	-0.30	<0.0001
BMI	0.15	0.002	-0.11	0.023	-0.32	<0.0001
% fat	0.15	0.003	-0.11	0.021	-0.32	<0.0001
BMI, % fat, waist	0.12	0.014	-0.09	0.067	-0.31	<0.0001

*Sex controlled for in all correlations. VO_{2max} is in ml · kg⁻¹ · min⁻¹.

predictor of ISI and insulin AUC, as shown in Table 2. The strength of this relationship was evident even after controlling for BMI, percent fat, and VO_{2max}, with higher waist circumferences values signifying greater degrees of insulin resistance (i.e., lower ISI and higher insulin AUC). In contrast, neither BMI nor percent fat retained its association with insulin resistance once waist circumference was statistically controlled. Interestingly, the relationship between VO_{2max} and ISI remained significant after controlling for all other factors, but these associations were weaker than those for waist circumference. Because of the influence of race on body composition and diabetes risk, we also performed the correlation analyses controlling for race and did not observe any race effects. We also explored the potential impact of the different body composition assessment methods, and found that the correlation between ISI and percent fat was very similar among subjects assessed using DXA ($r = -0.392, P < 0.0001, n = 270$) and those assessed using hydrostatic weighing ($r = -0.407, P < 0.001, n = 131$).

The relative importance of central adiposity and fitness became more evident when multiple stepwise linear regression analyses were performed. After entering age, BMI, percent fat, waist circumfer-

ence, and VO_{2max} into the model, only waist circumference and VO_{2max} explained a significant portion of ISI (27.7 and 1.9%, respectively) (Table 3). Similarly, waist circumference was the most important predictor of insulin AUC, explaining 18.9% of the variance, whereas VO_{2max} explained only 1.2% and age 1.7%. VO_{2max} was the strongest predictor of glucose AUC (10.9%), with waist circumference explaining 8.4%.

The additive impact of waist circumference and VO_{2max} on ISI is depicted in Fig. 1. Two-way (waist circumference tertile and VO_{2max} tertile) ANOVA determined significant main effects for waist circumference ($P < 0.001$) and VO_{2max}

($P = 0.050$) in the absence of an interaction ($P = 0.23$). Specifically, as waist circumference tertiles increased from small to large, a stepwise decrement in ISI was observed: small waist = 6.7 ± 3.5 (ISI, nontransformed); medium waist = 4.8 ± 2.2 ; large waist = 3.6 ± 2.0 ($P < 0.001$ for all comparisons), indicating increasing insulin resistance with increasing waist circumference. Although the relationship between VO_{2max} and ISI was less robust, there was a clear increase in ISI from low fitness (4.4 ± 2.3) to moderate fitness ($5.4 \pm 3.2; P = 0.030$), with no additional increase from moderate to high fitness (5.3 ± 3.3).

Age

Age was not associated with either ISI ($r = -0.015, P = 0.760$) or insulin AUC ($r = -0.04, P = 0.372$), although glucose AUC did increase with increasing age ($r = 0.33, P < 0.0001$). The relationship between age and measures of adiposity was variable; age was inversely associated with BMI ($r = -0.11, P = 0.023$) and percent fat ($r = -0.13, P = 0.009$), but only a weak trend was observed with waist circumference ($r = -0.08, P = 0.092$). As expected, VO_{2max} declined with advancing age in both women ($r = -0.71$) and men ($r = -0.83; both P < 0.0001$). We further explored the impact of age by dichotomizing the sample into those aged <75 years ($n = 268$) or >75 years ($n = 139$). Compared with the younger group, subjects >75 years had significantly ($P < 0.0001$) lower VO_{2max}, higher glucose AUC, and a trend ($P = 0.076$) for lower percent fat. The significance of the correlations between ISI and BMI, percent fat, and waist circumference were the same in the younger and older groups (all $P < 0.0001$), although the r value was attenuated for BMI and waist circumference in the older group.

Table 3—Independent predictors of insulin resistance resulting from multiple stepwise linear regression analysis

	ISI	Insulin AUC	Glucose AUC
Waist circumference	*0.277 ₁	0.189 ₁	0.084 ₂
VO _{2max}	0.019 ₂	*0.012 ₂	
Age		0.017 ₃	0.109 ₁
Total r ²	0.296	0.218	0.194

The analysis included predictors from Table 2 and retained variables with P values <0.10. Note: sex, BMI, and % fat were not retained in the model because they were not significant predictors. Values in the table represent the independent contributions to r² for each predictor variable in the model. AUC is the area under the curve during the OGTT, * denotes negative correlation, and subscripts indicate the order of entry into the regression model. Log-transformed values for ISI, insulin AUC, and glucose AUC were used for these analyses.

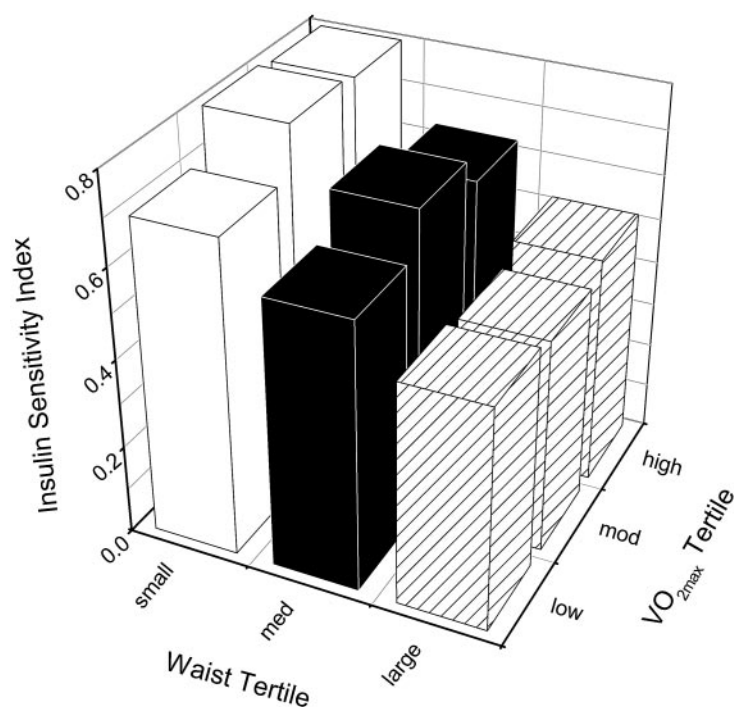


Figure 1—Tertiles of waist circumference (small, white bars; medium, black bars; large, striped bars) and VO_{2max} ($ml \cdot kg^{-1} \cdot min^{-1}$) in relation to the ISI (log transformed).

CONCLUSIONS— The results of this study indicate that both fitness and fatness continue to play important and opposing roles in either protecting against or contributing to insulin resistance in the latter half of the lifespan, but that abdominal adiposity, estimated by waist circumference, has the greatest influence. The unique aspects of this analysis were the inclusion of 139 adults aged 75 years and older, combined with the measures of fitness and adiposity (rather than reliance on self-report).

In agreement with our results, Christou et al. (19) observed that waist circumference, BMI, and total body fat were better predictors of insulin sensitivity, assessed with an intravenous glucose tolerance test, than VO_{2max} in 135 men aged 20–79. Similarly, Clevenger et al. (20) reported that intravenous glucose tolerance test–derived insulin sensitivity was inversely related to waist circumference in 126 adults ($r = -0.48$). Furthermore, insulin sensitivity was not dependent upon age among their sedentary subjects after controlling for whole-body adiposity (although a different relationship was observed among endurance-trained adults). However, the “older” subjects in the latter study were only 59 ± 1 years, the maximum age was 80 years, and the sample of older sedentary subjects was relatively small ($n = 43$). Although limited pub-

lished data are available for the elderly, an elegant study by Paolisso et al. (21) demonstrated that whole-body glucose disposal among centenarians (102 ± 1 years, $n = 14$), assessed during euglycemic clamps, was comparable to that of adults aged 45 ± 2 years ($n = 20$), and greater than that of adults aged 78 ± 1 years ($n = 22$). BMI of the centenarians was lower than that in the other two groups. These results provide additional evidence that advancing age does not necessarily result in insulin resistance.

Our study contributes to the ongoing debate as to whether fitness or fatness is a more important determinant of health risk. Data from 68,500 U.S. adults in the National Health Interview Survey (22) indicate that the odds ratio for diabetes among physically active adults was 1.65 among those who were overweight, 3.62 among those in obese class I and II, and 8.37 among those in obese class III, compared with normal-weight adults. The risks were significantly elevated among inactive adults in each BMI category, relative to active adults in the same BMI category. These results indicate that although a physically active lifestyle helps protect against the development of type 2 diabetes, it is not sufficient to counter the adverse consequences of overweight and obesity. The limitation of that sample was that all data were self-reported. In studies

in which fitness and adiposity were measured, there is intriguing evidence that higher levels of fitness prevent the weight-related morbidity and mortality associated with diabetes (23,24). Our results support fitness as a significant component of overall health, which impacts not only insulin resistance, but also whole-body and abdominal adiposity. As shown by Wong et al. (25), middle-aged men with higher cardiorespiratory fitness have less abdominal adiposity and smaller waist circumferences, independent of BMI. Nevertheless, our data indicate that abdominal adiposity, as reflected by waist circumference, is superior to fitness in predicting insulin resistance among middle-aged, older, and very old adults.

There is less debate regarding the independent contribution of abdominal adiposity to risk factors for cardiovascular disease and type 2 diabetes. Prospective studies have shown that elevated waist circumference (>88 cm in women and >102 cm in men) was associated with a greater risk of development of type 2 diabetes among 1,968 white and Mexican-American adults (14) and was associated with a greater number of metabolic disorders within an individual. Cross-sectional studies of postmenopausal women and men up to 84 years of age demonstrate similar associations between a high waist circumference and hyperinsulinemia, hypertriglyceridemia (26), insulin resistance (27), and other metabolic risk factors, including low HDL₂ cholesterol (28), a protective factor against cardiovascular disease.

Our observation that percent fat was inversely associated with age is consistent with data from the National Health and Nutrition Examination Survey (NHANES) III, in which fat mass increased until about age 60 and then began to decline (29). Furthermore, our finding that men were more insulin resistant than women, despite being matched on age and BMI, also is consistent with data from NHANES III and NHANES 1999–2000, in which impaired fasting glucose was more prevalent among men than among women (30). This phenomenon may be attributable to the central location of adipose tissue in men. As expected, the men in our sample had less total fat mass and a lower percentage of body fat, but a larger waist circumference than the women, supporting the contribution of abdominal fat to insulin resistance.

Our analysis did have limitations, the greatest being the potential confounding

effects of medication use (e.g., ACE inhibitors, β -blockers, and diuretics). The subjects in our sample were taking a variety of prescription and over-the-counter medications, some of which may have had insulin-sensitizing effects, whereas others probably had desensitizing effects. Because many of the older subjects were taking more than one medication each and because the medication classes and doses varied, it was not possible to weigh the relative impact of sensitizer and desensitizer drugs within an individual. Therefore, we chose not to control for medication use.

In summary, results of the current analysis highlight the importance of abdominal adiposity, evaluated using waist circumference, as a risk factor for insulin resistance in 50- to 95-year-old women and men. Fitness was also a significant predictor of insulin resistance into old age, but was less robust than waist circumference. It is evident that lifestyle behaviors that contribute to smaller waist circumference and greater fitness continue to protect against the development of insulin resistance, even into the 10th decade of life. Furthermore, our results support the measurement of waist circumference in routine clinical practice as an efficient, economical, and valid tool for assessing adiposity-related health risk.

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