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Association of low adiponectin levels with the metabolic syndrome—the Chennai Urban Rural Epidemiology Study (CURES-4)

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Abstract

The aim of the study was to assess the relation of adiponectin levels with the metabolic syndrome in Asian Indians, a high-risk group for diabetes and premature coronary artery disease. The study was conducted on 100 (50 men and 50 women) type 2 diabetic subjects and 100 age and sex matched subjects with normal glucose tolerance selected from the Chennai Urban Rural Epidemiology Study, an ongoing population study in Chennai in southern India. Metabolic syndrome was defined using modified Adult Treatment Panel III (ATPIII) guidelines. Adiponectin values were significantly lower in diabetic subjects (men: 5.2 vs 8.3 μg/mL, $P = .00l$; women: 7.6 vs 11.1 μg/mL, $P < .00l$) and those with the metabolic syndrome (men: 5.0 vs 6.8 μg/mL, $P = .01$; women: 6.5 vs 9.9 μg/mL, $P = .001$) compared with those without. Linear regression analysis revealed adiponectin to be associated with body mass index ($P < .05$), waist circumference ($P < .01$), fasting plasma glucose ($P = .001$), glycated hemoglobin ($P < .001$), triglycerides ($P < .00l$), high-density lipoprotein (HDL) cholesterol ($P < .001$), cholesterol/HDL ratio ($P < .00l$), and insulin resistance measured by homeostasis assessment model ($P < .00l$). Factor analysis identified 2 factors: factor 1, negatively loaded with adiponectin and HDL cholesterol and positively loaded with triglycerides, waist circumference, and insulin resistance measured by homeostasis assessment model; and factor 2, with a positive loading of waist circumference and systolic and diastolic blood pressure. Logistic regression analysis revealed adiponectin to be negatively associated with metabolic syndrome (odds ratio [OR], 0.365; $P < .001$) even after adjusting for age (OR, 0.344; $P < .00l$), sex (OR, 0.293; $P < .001$), and body mass index (OR, 0.292; $P < .00l$). Lower adiponectin levels are associated with the metabolic syndrome per se and several of its components, particularly, diabetes, insulin resistance, and dyslipidemia in this urban south Indian population.

1. Introduction

An increased predisposition of Asian Indians to diabetes and other components of the metabolic syndrome is well known [1-5]. According to a World Health Organization (WHO), India already leads the world in the number of patients with and would contribute more than 20% of the world's diabetic population by 2025 [3]. Migrant Indian studies have shown that for any given body mass index (BMI), Indians have higher body fat, higher plasma insulin levels, and greater insulin resistance compared with Europeans [6,7]. Thus, it is worthwhile to look at factors associated with diabetes and insulin resistance in Indians. In this respect, adiponectin, low levels of which have been linked to components of metabolic syndrome, is of great interest [8-12]. There are no studies looking at the association of adiponectin levels with the metabolic syndrome in Asian Indians and hence this study.

2. Materials and methods

A total of 100 diabetic subjects (50 men + 50 women) and 100 age- and sex-matched normal glucose tolerance (NGT) subjects were recruited for the study.

Study subjects were selected from the urban component of the Chennai Urban Rural Epidemiology Study (CURES), an ongoing epidemiological study conducted on a representative population (aged $\geq$20 years) of Chennai (formerly Madras), the fourth largest city in India. The methodology of the study has been published elsewhere [13]. Briefly, in phase I of CURES, 26 001 individuals were recruited based on a systematic random sampling technique. Self-reported

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diabetic subjects on drug treatment of diabetes were classified as "known diabetic subjects." Fasting capillary blood glucose was determined in all subjects using a One-Touch Basic glucometer (Lifescan, Milpitas, Calif, USA).

In phase 2 of CURES, all the known diabetic subjects (n= 1529) were invited to the center for detailed studies. In addition, age- and sex-matched nondiabetic subjects (fasting capillary blood glucose of <100 mg/dL) and all subjects with fasting capillary blood glucose of ≥110 mg/dL based on American Diabetes Association (ADA) fasting criteria [14] underwent oral glucose tolerance tests using 75-g oral glucose load dissolved in 250 mL of water. Those who were confirmed by oral glucose tolerance test to have 2-hour plasma glucose value of ≥200 mg/dL based on WHO consulting group criteria [15] were labeled as "newly detected diabetic subjects." Subjects who had fasting plasma glucose of <110 mg/dL and 2-hour plasma glucose value of <140 mg/dL were categorized as NGT subjects.

Institutional ethical committee approval was obtained, and informed consent was obtained from all study subjects.

Physical examination included height, weight, and waist and hip measurements using standardized techniques. Obesity was defined as BMI ≥25 kg/m^2 for both men and women using Asia Pacific WHO guidelines [16].

A fasting blood sample was taken, and serum was separated and stored at −70°C until the assays were performed. Fasting plasma glucose (glucose oxidase-peroxidase method, product catalogue no. 1448668, Roche Diagnostics, Mannheim, Germany) [17] serum cholesterol (cholesterol oxidase-peroxidase-amidopyrine method, product catalogue no. 11489232, Roche Diagnostics) [18], serum triglycerides (glycerol phosphate oxidase-peroxidase-amidopyrine method, product catalogue no. 1148872, Roche Diagnostics) [19], and high-density lipoprotein (HDL) cholesterol (direct method polyethylene glycol–pretreated enzymes, product catalogue no. 03030024, Roche Diagnostics) [20] were measured using Hitachi-912 Autoanalyser (Hitachi, Germany). The intra-assay and interassay coefficient of variation for the biochemical assays ranged between 3.1% and 7.6%. Low-density lipoprotein (LDL) cholesterol was calculated using the formula of Friedewald et al [21]. Glycated hemoglobin (HbA1C) was estimated by high-pressure liquid chromatography using the Variant machine (Bio-Rad, Hercules, Calif, USA). The intra-assay and interassay coefficient of variation of HbA1C was <10%. Serum insulin concentration was estimated using enzyme-linked immunosorbent assay (catalogue no. K6219, Dako, Glostrup, Denmark). The intra-assay and the interassay coefficients of variation for insulin assay were 5.7% and 8.9%, respectively, and the lower detection limit was 0.5 μIU/mL.

Hypercholesterolemia (serum cholesterol ≥200 mg/dL), hypertriglyceridemia (serum triglycerides ≥150 mg/dL), and low HDL levels (men: HDL cholesterol <40 mg/dL; women: HDL cholesterol <50 mg/dL) were diagnosed based on ATPIII guidelines [22]. Insulin resistance was calculated using the homeostasis assessment (HOMA IR) Model using the formula: fasting insulin (μIU/mL) × fasting plasma glucose (mmol/L)/22.5 [23]. Normal glucose tolerance subjects whose HOMA IR values exceeded 1.93 (this cutoff value of 1.93 was derived based on the European Group of Insulin Resistance criteria [24] for insulin resistance which is the 75th percentile of HOMA IR value in the total study population in the Chennai Urban Population Study [25]) were considered to have insulin resistance.

Metabolic syndrome was diagnosed based on modified ATPIII guidelines [22] if 3 or more of the following were present: abdominal obesity (definition of abdominal obesity was modified using Asia Pacific WHO guidelines as waist circumference of ≥90 cm for men and ≥80 cm for women [16]), hypertension (subjects who were on antihypertensive medication and/or had systolic pressure of ≥130 mm Hg and/or diastolic blood pressure of ≥85 mm Hg), glucose intolerance (fasting plasma glucose of ≥110 mg/dL), hypertriglyceridemia (fasting triglycerides of ≥150 mg/dL), or low HDL cholesterol (HDL cholesterol of <40 mg/dL for men and <50 mg/dL for women).

Fasting adiponectin levels were measured using radioimmunoassay (catalogue no. HADP-61HK, Linco Research, St Charles, Mo, USA). The intra-assay and the interassay coefficients of variation were 3.8% and 7.4%, respectively, and the lower detection limit was 1 ng/mL.

3. Statistical analysis

One-way analysis of variance or Student *t* test was used to compare groups for continuous variables and χ^2 test or Fisher exact test to compare proportions. Diabetic subjects (men: n = 2; women: n = 4) on insulin therapy were excluded for analysis of HOMA IR. Adiponectin values and HOMA IR were log-transformed to obtain a normal distribution. Regression analysis was carried out using log-transformed adiponectin as the dependent variable and other risk factors as independent variables. Factor analysis was done to determine the relation of adiponectin with the components of metabolic syndrome by extracting the initial components by principal component analysis, followed by rotation of principal components by varimax method. Factors with loading >±0.3 were used to define a significant relationship. All analyses were done using Windows-based SPSS statistical package (version 10.0, Chicago), and *P* values <.05 were considered of significant.

4. Results

Table 1 shows the clinical and biochemical features of the study groups.

Mean adiponectin values in the total population were 6.75 μg/mL (geometric mean). The mean adiponectin level in women (7.9 μg/mL) was significantly higher than in men (5.4 μg/mL) ($P < .001$). The 25th percentile adiponectin value was 4.4 μg/mL in men and 5.9 μg/mL in women,

Table 1
Clinical and biochemical characteristics of the study groups

Parameters	Men		Women	
	No DM (n = 50)	DM (n = 50)	No DM (n = 50)	DM (n = 50)
Age (y)	47 ± 11	48 ± 12	45 ± 12	48 ± 10
Waist (cm)	88 ± 12	94 ± 9*	84 ± 12	95 ± 11***
BMI (kg/m^2)	23.2 ± 3.8	25.6 ± 4.0*	24.5 ± 5.2	26.7 ± 4.6*
Systolic blood pressure (mm Hg)	122 ± 15	128 ± 16	118 ± 15	129 ± 17.0**
Diastolic blood pressure (mm Hg)	80 ± 10	82 ± 9	75 ± 10	80 ± 13*
Fasting plasma glucose (mg/dL)	88 ± 11	157 ± 58***	85 ± 9	167 ± 65***
Total cholesterol (mg/dL)	188 ± 42	200 ± 42	189 ± 38	198 ± 35
Serum triglycerides (mg/dL)	133 ± 62	221 ± 168***	150 ± 44	168 ± 97***
Serum HDL cholesterol (mg/dL)	42 ± 11	38 ± 8	50 ± 8	42 ± 8***
Serum LDL cholesterol (mg/dL)	123 ± 35	115 ± 42	119 ± 35	123 ± 38
Cholesterol/HDL ratio	4.7 ± 1.2	5.3 ± 1.3*	4.0 ± 1.0	5.0 ± 1.2***
HbA1C (%)	5.9 ± 0.6	8.9 ± 2.1***	5.7 ± 0.5	9.0 ± 1.9***
Log-transformed HOMA IR (GM)	1.4	2.9***	1.4	3.5***
Treatment for diabetes, n (%)				
None	–	5 (10%)	–	4 (8%)
Diet alone	–	1 (2%)	–	1 (2%)
OHA	–	42 (84%)	–	41 (82%)
Insulin	–	1 (2%)	–	2 (4%)
OHA + insulin	–	1 (2%)	–	2 (4%)

Data are mean values ± SD. No DM indicates nondiabetic subjects; DM, diabetic subjects; GM, geometric mean; OHA, oral hypoglycemic agent.
* $P < .05$ compared with No DM.
** $P < .01$ compared with No DM.
*** $P < .001$ compared with No DM.

whereas the 75th percentile values were 8.6 and 12.0 μg/mL, respectively.

Serum adiponectin values were significantly lower in diabetic compared with nondiabetic subjects both in men (5.2 vs 8.3 μg/mL, $P = .001$) and women (7.6 vs 11.1 μg/mL, $P < .001$) diabetic vs nondiabetic subjects, respectively (Fig. 1A).

Logistic regression analysis using diabetes as the dependent variable and adiponectin as independent variable revealed adiponectin to be negatively associated with

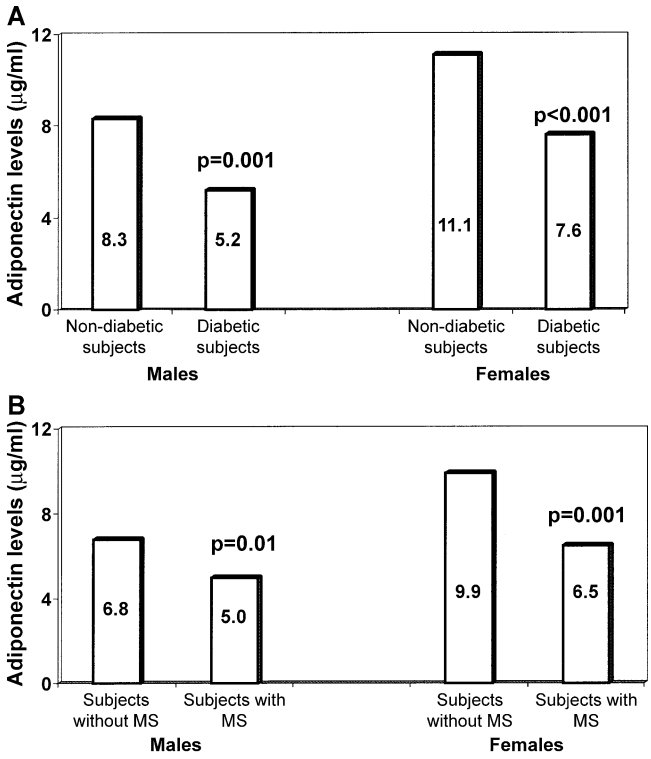

Fig. 1. Adiponectin values in study groups. A, In subjects with and without diabetes. B, In subjects with and without metabolic syndrome.

Table 2
Simple and multivariate regression analysis using log-transformed adiponectin as dependent variable

	$\beta 1$	$\beta 2$	$\beta 3$
BMI	−.111	−.144*	−.147*
Waist circumference	−.219**	−.203**	−.217**
Systolic blood pressure	−.014	−.006	−.038
Diastolic blood pressure	−.082	−.048	−.065
Fasting plasma glucose	−.259***	−.269***	−.271***
HbA1c	−.281***	−.278***	−.286***
Cholesterol	.057	.052	.041
Triglycerides	−.336***	−.302***	−.295***
HDL cholesterol	.424***	.390***	.379***
LDL cholesterol	.141*	.131	.120
Cholesterol/HDL ratio	−.289***	−.250***	−.243***
Log-transformed HOMA IR	−.339***	−.337***	−.349***

$\beta 1$ indicates simple standardized regression coefficient; $\beta 2$, multivariate standardized linear regression coefficient adjusted for sex; $\beta 3$, multivariate standardized linear regression coefficient adjusted for sex and age.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

diabetes (odds ratio [OR], 0.243; 95% confidence interval [CI], 0.136-0.435; $P < .00l$]. This association persisted even after adding BMI into the equation (OR, 0.254; 95% CI, 0.140-0.460; $P < .00l$).

Nondiabetic men with insulin resistance had significantly lower adiponectin values compared with those without (men with insulin resistance: 4.8 μg/mL vs without insulin resistance: 7.5 μg/mL, $P < .001$), whereas in women, the difference did not reach statistical significance (women with insulin resistance: 7.5 μg/mL vs without insulin resistance: 9.2 μg/mL, $P = .076$).

Men with obesity had significantly lower adiponectin levels compared with those without (obese: 4.9 μg/mL vs nonobese: 6.1 μg/mL, $P = .023$), but this difference was not seen in women (obese: 7.8 μg/mL vs nonobese: 8.0 μg/mL, $P = .915$). Both men (5.5 vs 6.2 μg/mL, $P = .246$; subjects with abdominal obesity vs subjects without abdominal obesity, respectively) and women (7.5 vs 9.3 μg/mL, $P = .135$; subjects with abdominal obesity vs subjects without abdominal obesity, respectively) with abdominal obesity had slightly lower adiponectin values compared with those without. This difference did not reach statistical significance.

There was no significant difference in the adiponectin levels between hypertensive and normotensive subjects (men: hypertensive 5.5 μg/mL vs normotensive 6.1 μg/mL, $P = .305$; women: hypertensive 7.7 μg/mL vs normotensive 8.1 μg/mL, $P = .649$),

Adiponectin levels were significantly lower in subjects with hypertriglyceridemia both in men (hypertriglyceridemia: 5.0 μg/mL vs normal triglycerides: 6.7 μg/mL, $P = .009$) and women (hypertriglyceridemia: 6.7 μg/mL vs normal triglycerides: 8.6 μg/mL, $P = .05$). Women with low HDL levels had lower adiponectin levels compared with those with normal HDL levels (low HDL levels: 6.7 μg/mL vs normal HDL levels: 11.0 μg/mL, $P < .001$). However, the difference in adiponectin did not reach statistical significance in men (low HDL levels: 5.4 μg/mL vs normal HDL levels: 6.4 μg/mL, $P = .173$).

There were no significant differences in adiponectin levels between hypercholesterolemic and normocholesterolemic subjects (men: 5.2 vs 6.3 μg/mL, $P = .117$; women: 9.2 vs 7.1 μg/mL, $P = .054$, hypercholesterolemia vs normocholesterolemic subjects, respectively) or between those with high and normal LDL levels (men: 5.6 vs 6.4 μg/mL, $P = .295$; women: 8.7 vs 6.5 μg/mL, $P = .058$, high LDL vs normal LDL, respectively).

Eighteen (18%) nondiabetic subjects (11 men, 7 women) and 88 (88%) diabetic subjects (40 men, 48 women) were diagnosed to have metabolic syndrome according to modified ATPIII guidelines. Serum adiponectin values were significantly lower in subjects with the metabolic syndrome compared with those without (men: 5.0 vs 6.8 μg/mL, $P = .01$; women: 6.5 vs 9.9 μg/mL, $P = .001$) (Fig. 1B).

Logistic regression analysis revealed adiponectin to be negatively associated with metabolic syndrome (OR, 0.365; 95% CI, 0.216-0.618; $P < .001$) even after adjusting for age (OR, 0.344; 95% CI, 0.201-0.589; $P < .001$), sex (OR, 0.293; 95% CI, 0.164-0.524; $P < .001$), and BMI (OR, 0.292; 95% confidence interval, 0.157-0.562; $P < .001$).

Adiponectin values decreased significantly with increase in number of the components of metabolic syndrome (normal subjects [without metabolic syndrome]: 11.0 μg/mL [n = 16], those with 1 component of the syndrome: 9.03 μg/mL [n = 30], those with 2 components: 6.90 μg/mL [n = 48], and those with 3 components: 5.76 μg/mL [n = 106]; analysis of variance, $P = .001$). Diabetic subjects with metabolic syndrome had significantly lower adiponectin levels compared with nondiabetic subjects with metabolic syndrome (5.5 vs 7.5 μg/mL, $P = .045$).

Table 2 presents simple and multivariate regression analysis using log-transformed adiponectin as the dependent variable and various components of the metabolic syndrome as independent variables. Adiponectin showed a significant negative association with BMI ($P < .05$), waist circumference ($P < .01$), fasting plasma glucose ($P < .001$), HbA1c ($P < .001$), triglycerides ($P < .001$), total cholesterol/HDL ratio ($P < .001$), and HOMA IR ($P < .001$) even after

Table 3
Factor loading pattern of adiponectin after varimax rotation of principle components in total study population

Phenotype	Factor loadings	
	Factor 1	Factor 2
Systolic blood pressure	−0.050	0.894
Diastolic blood pressure	0.076	0.888
Waist circumference	0.476	0.466
Serum triglycerides	0.588	0.190
HDL cholesterol	−0.754	0.098
Log-transformed adiponectin	−0.734	0.056
Log-transformed HOMA IR	0.733	0.151
% Of variance	34.92	23.71

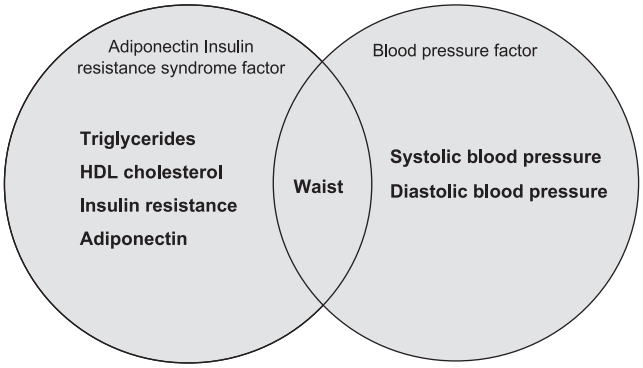

Fig. 2. Clustering pattern of metabolic abnormalities with adiponectin.

adjusting for sex and age and positive association with HDL cholesterol ($P < .001$) (Table 2).

In the total study population, 2 factors explained 58.6% of the variance. Factor 1, which represents the adiponectin–insulin resistance syndrome factor, was negatively loaded with adiponectin and HDL cholesterol and positively loaded with waist circumference, triglycerides, and HOMA IR. Factor 2, the blood pressure factor, was positively loaded with waist circumference and systolic and diastolic blood pressure (Table 3 and Fig. 2). The factors clustered in a similar pattern when the analysis was performed in NGT subjects alone, whereas in the diabetic subjects, the adiponectin–insulin resistance syndrome factor had all the components similar to the total study population except for waist circumference (data not shown).

5. Discussion

This is the first study to report on the association of adiponectin with the metabolic syndrome in an Asian Indian population and is significant because of the hyperinsulinemia and greater insulin resistance consistently reported in this population [4,5].

We observed that diabetic subjects had relatively lower levels of adiponectin, which is consistent with earlier cross-sectional and prospective studies [8,9]. We also found a negative association between adiponectin and triglycerides and a positive association with HDL cholesterol. An earlier report, which examined the association of lipids with adiponectin, has suggested central adiposity as the link between adiponectin and dyslipidemia and insulin resistance [26]. This is supported by an association between obesity indices such as BMI and waist circumference noted in this study and other studies [27-29].

There are, however, very few studies, which have looked at the association of adiponectin with metabolic syndrome per se [30,31]. Choi et at [31] in a prospective study on 372 Koreans reported adiponectin values to be strongly associated with diabetes and metabolic syndrome as observed in this study. In the study by Hulthe et al [32], subjects with 1 risk factor had lower adiponectin values compared with normal subjects, and the values were even lower in subjects with metabolic syndrome. This is in agreement with our study where adiponectin values decreased with increase in number of metabolic abnormalities. Furthermore, metabolic syndrome defined using the modified ATPIII guidelines showed a strong negative association with adiponectin levels, even after adjusting for age and sex.

HOMA IR, an index of insulin resistance, was strongly associated with adiponectin, which persisted even after adjusting for age and sex. Furthermore, we used factor analysis to determine the insulin resistance cluster and found that adiponectin clusters with insulin resistance, waist circumference, triglycerides, and HDL cholesterol. This is similar to that reported by Hanley et a1 [33], where the adiponectin clustered with HDL cholesterol, triglycerides, waist circumference, and insulin. In addition, we also observed a strong negative correlation between insulin resistance and adiponectin. This supports the insulin-sensitizing effect of adiponectin. Furthermore, the positive association with HDL cholesterol suggests that the anti-atherogenic effect of adiponectin could probably be mediated through increased HDL level [33,34]. However, blood pressure clustered into a separate factor as observed in the study of Meigs et al [35] and did not show an association with adiponectin [35,36].

Ethnic differences have been earlier reported in adiponectin levels, with African Americans having lower values [27,37]. In recent study by Abate et al [38], Asian Indians were reported to have lower adiponectin value compared with whites. In this context, our study results are of interest as they suggest a good association between adiponectin and metabolic syndrome in Asian Indians. These findings allow us to generate a hypothesis that the unexplained high degree of insulin resistance observed in Asian Indians could probably be caused by lower adiponectin levels, and this could be tested in prospective multinational studies. It is also of interest that adiponectin showed a strong association with HDL cholesterol, levels of which have been reported to be much lower among Asian Indians compared with other ethnic groups [39]. Thus, we speculate that decreased adiponectin could be one of the reasons for the increased insulin resistance and high rates of metabolic syndrome and could at least in part explain the excess of premature coronary artery disease [40] consistently reported in Asian Indians.

One of the limitations of the study is that it is a cross-sectional one, which is not an appropriate design to assess the cause-and-effect relationship between adiponectin and metabolic syndrome. However, the strengths of the study are that it is population-based and done on a representative sample of the population.

In summary, we have examined the association of adiponectin with the metabolic syndrome in an urban South Indian population known to have very high prevalence of diabetes, insulin resistance, and coronary artery disease. We observed that lower serum adiponectin levels are associated with the metabolic syndrome and its various components, particularly, insulin resistance and diabetes in this population.

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