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ORIGINAL ARTICLE

Monocyte-HDL Ratio: Can It Be Included in the Follow-Up of Diabetes Mellitus and Diagnosis of Diabetic Nephropathy?

Monosit-HDL Oranı: Diyabetik Hastaların Takibinde ve Diyabetik Nefropatinin Tanısında Kullanılabilir mi?

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ABSTRACT

Background and Aim: Diabetic nephropathy is the most common cause of end-stage renal disease and albuminuria is the earliest manifestation of diabetic nephropathy. Oxidative stress and inflammation caused by advanced glyco-oxidation end products contribute to micro and macrovascular complications of diabetes. Monocyte to high-density lipoprotein (HDL) cholesterol ratio (MHR) is an essential indicator of inflammation and oxidative stress. In this study, we aimed to reveal the relationship between diabetes regulation and complications and MHR.
Material and Method: A total of 182 subjects, including 152 patients with diabetes mellitus (DM) and 30 healthy controls, were included in this study. All data of the subjects were scanned retrospectively. The DM group was divided into two groups; nephropathy (n=68) and non-nephropathy (n=84), with a limit of 30 mg/day for albuminuria. MHR was calculated by dividing the monocyte count by the HDL cholesterol count.
Results: When patients with DM were divided into nephropathy and non-nephropathy, patients with nephropathy had higher MHR levels than the other group. We showed that MHR correlated with albuminuria, creatinine, and HbA1c in patients with diabetic nephropathy. In addition, in the regression analysis, albuminuria and MHR were predictors of DN, while MHR, age, and creatinine were found as independent predictors of albuminuria.
Conclusion: MHR, which is an easily calculated marker with simple laboratory tests and frequently requested in routine practice in the follow-up of diabetes patients, can help predict the regulation of diabetes and its kidney complications.

Keywords: Albuminuria, diabetic nephropathy, inflammation, monocyte-hdl cholesterol ratio

ÖZ

Giriş ve Amaç: Diyabetik nefropati, son dönem böbrek hastalığının en yaygın nedenidir ve albüminüri, diyabetik nefropatinin en erken belirtisidir. İleri gliko-oksidasyon son ürünlerinin neden olduğu oksidatif stres ve inflamasyon, diyabetin mikro ve makrovasküler komplikasyonlarına katkıda bulunur. Monosit sayısının, yüksek yoğunluklu lipoprotein (HDL) kolesterol seviyesine oranı (MHR), inflamasyon ve oksidatif stresin önemli bir göstergesidir. Çalışmada, diyabet regülasyonu ve komplikasyonlarıyla MHR arasındaki ilişkinin ortaya çıkarılması amaçlanmıştır.
Gereç ve Yöntem: Çalışmaya 152'si diabetes mellitus (DM) hastası ve 30'u sağlıklı kontrol olmak üzere toplam 182 kişi dahil edildi. Olguların tüm verileri retrospektif olarak tarandı. DM grubu albüminüri sınırı 30 mg/gün olmak üzere, nefropatisi olan (n=68) ve non-nefropatili (n=84) olmak üzere iki gruba ayrıldı. MHR, monosit sayısının HDL kolesterol sayısına bölünmesiyle hesaplandı.
Bulgular: DM'li hastalar nefropatik ve non-nefropatik olarak ayrıldığında, nefropatili hastaların MHR düzeyleri diğer gruba göre daha yüksekti. Diyabetik nefropatili hastalarda MHR'nin albüminüri, kreatinin ve HbA1c ile korele olduğunu gösterdik. Ayrıca regresyon analizinde albüminüri ve MHR DN'yi öngördürürken, MHR, yaş ve kreatinin düzeyi albüminürinin bağımsız ön görüdürücüleriydi.
Sonuç: Diyabet hastalarının takibinde rutin pratikte sıklıkla istenen ve basit laboratuvar testleri ile kolayca hesaplanabilen bir belirteç olan MHR, diyabetin hem regülasyonunda hem de böbrek komplikasyonlarını öngörmede faydalı bir belirteç olabilir.

Anahtar Kelimeler: Albüminüri, diyabetik nefropati, inflamasyon, monosit-HDL kolesterol oranı

Introduction

Diabetes Mellitus (DM) is a worldwide common chronic disease characterized by disorders in carbohydrate, lipid and protein metabolism, manifested by hyperglycemia, consisting of insulin deficiency or insulin resistance (1). The number of patients with diabetes is increasing day by day due to unhealthy and irregular nutrition in societies, and accordingly, the total number of patients with diabetes is expected to reach 366 million by 2030 (2). In addition to acute metabolic complications, chronic microvascular and macrovascular complications are important causes of early mortality and morbidity of the disease, and the incidence of brain, cardiovascular or renal vascular disease is higher in diabetic patients than in healthy individuals (3-4). Endothelial dysfunction and atherosclerosis have important effects on microvascular and macrovascular complications in diabetic patients. It is also known that oxidative stress and inflammation caused by advanced glyco-oxidation end products contribute to these complications (5). Diabetic nephropathy (DN), which is one of the microvascular complications seen in diabetic patients, is not only an important cause of morbidity and mortality but is also associated with a serious increase in the frequency of death due to cardiovascular causes (6).

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High-density lipoprotein HDL cholesterol (HDL) protects endothelial tissue from the harmful effects of low-density lipoprotein cholesterol (LDL) and also inhibits the oxidation of LDL. At the same time, HDL-C has anti-thrombotic, anti-inflammatory, and anti-oxidant effects. Decreased HDL level is an important risk factor for cardiovascular disease. HDL prevents atherosclerosis by transporting cholesterol from peripheral tissues to the liver (7-9). Monocytes are released from their bone marrow precursors into the circulation and migrate to tissues and differentiate into macrophages and dendritic cells. Macrophages are essential for the body's antimicrobial defense. Monocytes also contribute to local and systemic inflammation by producing inflammatory cytokines. The accumulation of monocytes and monocyte-derived macrophages in the walls of arteries has been shown to play a role in chronic inflammation, which plays a role in the development and progression of atherosclerosis, and even in the pathogenesis of diabetic nephropathy (10-12).

Recently, the monocyte/HDL ratio (MHR) has been thought to be a new marker of inflammation and oxidative stress due to the anti-inflammatory and antioxidant effects of HDL cholesterol as well as the proinflammatory effect of monocytes. There are various publications in the literature reporting that it is closely related to the presence and prognosis of some diseases. However, it has been used in a limited number of studies to determine whether it contributes to the etiopathogenesis of diabetic nephropathy (13-15). Therefore, in our study, we aimed to investigate whether there is a relationship between MHR and DN.

Material and method

Approval for this study was obtained from the Medical Ethics Committee of our hospital (Date and Ethics Committee No: 11/2022-4046-11838). All patients signed a written informed consent form. A total of 182 patients were included in the study, 152 of whom were in the DM group, and 30 were in the healthy control group. All patients' medical records (including information on sex, age, BMI, medications, duration of the disease the presence of retinopathy or neuropathy, biochemical blood lipid profiles and proteinuria levels) were reviewed retrospectively from our hospital's system.

The following were determined as inclusion criteria in the patient group. 1) Being between the ages of 18-65, 2) Having a history of previously diagnosed DM, 3) Having a known microvascular complication such as diabetic retinopathy or neuropathy. The criteria determined as exclusion criteria are; 1) Not being between the ages of 18-65, 2) Having a history of renal disease causing proteinuria other than diabetic nephropathy, 3) Having a history of inflammatory disease (auto-immune, rheumatological disease), 4) Malignant disease, 5) Receiving lipid-lowering treatment, 6) Taking glucocorticoid therapy 7) Being pregnant.

According to the 24-hour urine albuminuria levels of the patients; Those above 30 mg/day were divided into two groups: the diabetic nephropathy group (n=68) and those below 30 mg/day as the non-nephropathy group (n=84).

Biochemistry Laboratory of our institution was used in the study of biochemical analyzes. Serum c-reactive protein (CRP) levels were measured with an immunoturbidimetric assay using an automated clinical chemistry analyzer, and Jaffe Method was used for serum creatinine measuring. Total protein concentration levels in 24h urinary protein excretion were measured by a turbidometric assay using benzethonium chloride. The results were expressed as mg/L. MHR was calculated by dividing the monocyte count by the HDL cholesterol count.

Statistical analyses

Clinical and experimental data were analyzed using Statistical Package for Social Sciences for Windows version 21.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics for each variable were determined. Data were expressed as mean ± standard deviation or median and interquartile range (IQR). A statistically significant difference between the groups was determined by the $\chi 2$ test for categorical variables. Nonparametric statistics (Mann-Whitney U) and parametric statistics (independent sample t test) were all used for continuous variables. Associations between the variables were explored using Spearman's rho test. Binary logistic regression analysis was performed to determine independent predictors for diabetic nephropathy. Factors with a p value of <0.2 were included in the univariate analysis in the regression test while those that were significant in the univariate analysis were included in the multivariable evaluation. We also performed linear regression analysis to identify variables associated with albuminuria in patients with diabetic nephropathy. A statistically significant difference was considered when the p-value was <0.05.

Results

Demographic, clinical characteristics, and biochemical parameters of 152 patients with diabetes mellitus and 30 healthy control subjects are shown in Table 1. There were no significant differences with respect to the following variables between patients and control subjects; gender, serum levels of urea, alanine aminotransferase, triglyceride, LDL-C, white blood cell, hemoglobin, and platelet counts. The control group had significantly lower age, albuminuria, MHR, serum levels of creatinine, and HbA1c while serum HDL-C levels were significantly higher in this group.

In the bivariate correlation analysis of patients with diabetes, MHR was positively correlated with serum levels of HbA1c, urea, creatinine, and albuminuria ($r=0.211$, $p=0.009$, $r=0.245$, $p=0.002$,$r=0.487$, $p< 0.001$, $r=0.288$, $p < 0.001$, respectively) (Fig. 1 a–d).

We divided the patients with diabetes into two groups with and without diabetic nephropathy. There

were no significant differences with respect to the following variables between the two groups; age, gender, history of coronary artery disease, serum levels of alanine aminotransferase, triglyceride, HDL-C, LDL-C, hemoglobin, and platelet counts. Serum levels of urea, creatinine, HbA1c, white blood cell, and monocyte count were higher in patients with DN. In addition, albuminuria and monocyte HDL-C ratio were found statistically higher in this group (Table 2). In patients with diabetic nephropathy, albuminuria was positively correlated with creatinine and MHR while it was negatively correlated with HDL (r:0.277, p:0.022; r:0.361, p:0.002; r:-0.254, p:0.036, respectively). We also performed binomial logistic regression analysis to define variables that are independently associated with DN in patients with DM (Table 3). Age, gender, white blood cell, urea, creatinine, albuminuria, and MHR were included in this model. As a result of our multivariable analysis, albuminuria and MHR values were found as independent predictors of DN.

In addition, we performed linear regression analysis to define variables that are independently associated with albuminuria (Table 4). Age, gender, LDL-cholesterol, creatinine, hemoglobin A1C, and MHR were included in this model. Age, creatinine, and MHR were found as independent predictors of albuminuria in patients with DN.

Table 1. Demographic, clinic, and biochemical features of the patients with Diabetes Mellitus and healthy subjects

Parameters	Patients with DM (n=152) (Mean±SD), Median (IQR) or Frequency (n-%)	Healthy Subject (n=30) (Mean±SD), Median (IQR) or Frequency (n-%)	p
Age (years)	59.64 ± 10.05	50.13 ± 7.76	**0.011**
Female/Male	90/62	21/9	0.311
History of CAD	30 (19.7%)	---	---
Diabetic Nephropathy	68 (44.7%)	---	---
White blood cell count (10^3/µL))	8250.39 ± 2069.6	7720.34 ± 1497.27	0.069
Hemoglobin (gr/dl)	14.47 ± 1.63	14.11 ± 2.84	0.374
Platelet count (10^3/mm^3)	246 (89.5)	264 (89)	0.276
HbA1c (%)	7.85 ± 1.73	5.48 ± 0.32	**<0.001**
Urea (mg/dl)	30 (14)	27(11)	0.0672
Creatinine (mg/dL)	0.81 ± 0.29	0.73 ± 0.14	**0.018**
ALT (U/L)	18 (11)	23 (9)	0.217
LDL - cholesterol (mg/dL)	110.42 ± 31.16	117.17 ± 24.34	0.265
Triglyceride (mg/dl)	163 (85)	165.5 (126)	0.746
HDL-C cholesterol (mg/dL)	44 (13)	47 (11)	**0.01**
Albuminuria (mg/g)	15 (107)	5.5 (13)	**0.001**
MHR	14.13 (8.39)	11.37 (6.21)	**0.011**

CAD coronary artery disease, HbA1c hemoglobin A1c, ALT alanine aminotransferase, LDL-cholesterol low density lipoprotein cholesterol, HDL-cholesterol high density lipoprotein cholesterol, MHR monocyte-HDL ratio

Table 2. Demographic, clinic, and biochemical features of the patients with Diabetes Mellitus according to diabetic nephropathy groups

Parameters	Patients with DN (n=68) (Mean±SD), Median (IQR) or Frequency (n-%)	Patients without DN (n=84) Mean±SD), Median (IQR) or Frequency (n-%)	p
Age (years)	60.88 ± 10.93	58.67 ± 9.24	0.179
Female/Male	36/32	54/30	0.185
History of CAD	16	14	0.312
White blood cell count (10^3/µL)	8830.75 ± 2134.42	7887.05 ± 1929.16	**0.005**
Hemoglobin (gr/dl)	14.55 ± 1.54	14.41 ± 1.71	0.609
Platelet count (10^3/mm^3)	246 (99)	246 (87)	0.658
Monoycte (10^3/µL))	668.21 ± 205.24	557.53 ± 149.88	**<0.001**
HbA1c (%)	8.52 ± 1.77	7.32 ± 1.5	**<0.001**
Urea (mg/dl)	31 (19)	29.5 (11)	**0.003**
Creatinine (mg/dL)	0.9 ± 0.38	0.75 ± 0.18	**0.003**
ALT (U/L)	19 (10)	18 (12)	0.328
LDL - cholesterol (mg/dL)	107.84 ± 32.56	111.46 ± 30.06	0.366
Triglyceride (mg/dl)	168 (101)	157 (80)	0.515
HDL-cholesterol (mg/dl)	43 (14)	45 (15)	0.066
Albuminuria (mg/g)	137.5 (311)	0	**<0.001**
MHR	15.25 (8.5)	12.12(7.22)	**<0.001**

HbA1c hemoglobin A1c, ALT alanine aminotransferase, LDL-cholesterol low density lipoprotein cholesterol, HDL-cholesterol high density lipoprotein cholesterol, MHR monocyte HDL ratio

Table 3. Binomial Logistic Regression Analysis of diabetic nephropathy and other parameters in patients with DM

	Univariate Analysis		MultivariateAnalysis	
Parameters	OR (95% CI)	p value	OR (95% CI)	p value
Age (years)	1.023 (0.990-1.056)	0.179	-	-
Gender	1.676 (0.872-3.224)	0.122	-	-
White blood cell count (10^3/µL)	1.00 (1.00-1.00)	**0.007**	1.000 (0.999-1.001)	0. 820
HbA1c (%)	1.581 (1.258-1.987)	**<0.001**	1.828 (0.840-3.979)	0.129
Urea (mg/dl)	1.048 (1.017-1.080)	**0.002**	1.102 (0.945-1.285)	0.214
Creatinine (mg/dL)	7.169 (1.811-28.378)	**0.005**	0.066 (0.000-56.740)	0.430
Albuminuria (mg/g)	1.108 (1.069-1.148)	**<0.001**	1.083 (1.041-1.127)	**<0.001**
MHR	1.625 (1.393-1.896)	**<0.001**	2.005 (1.094-3.677)	**0.025**

HbA1c hemoglobin A1c, MHR monocyte HDL ratio

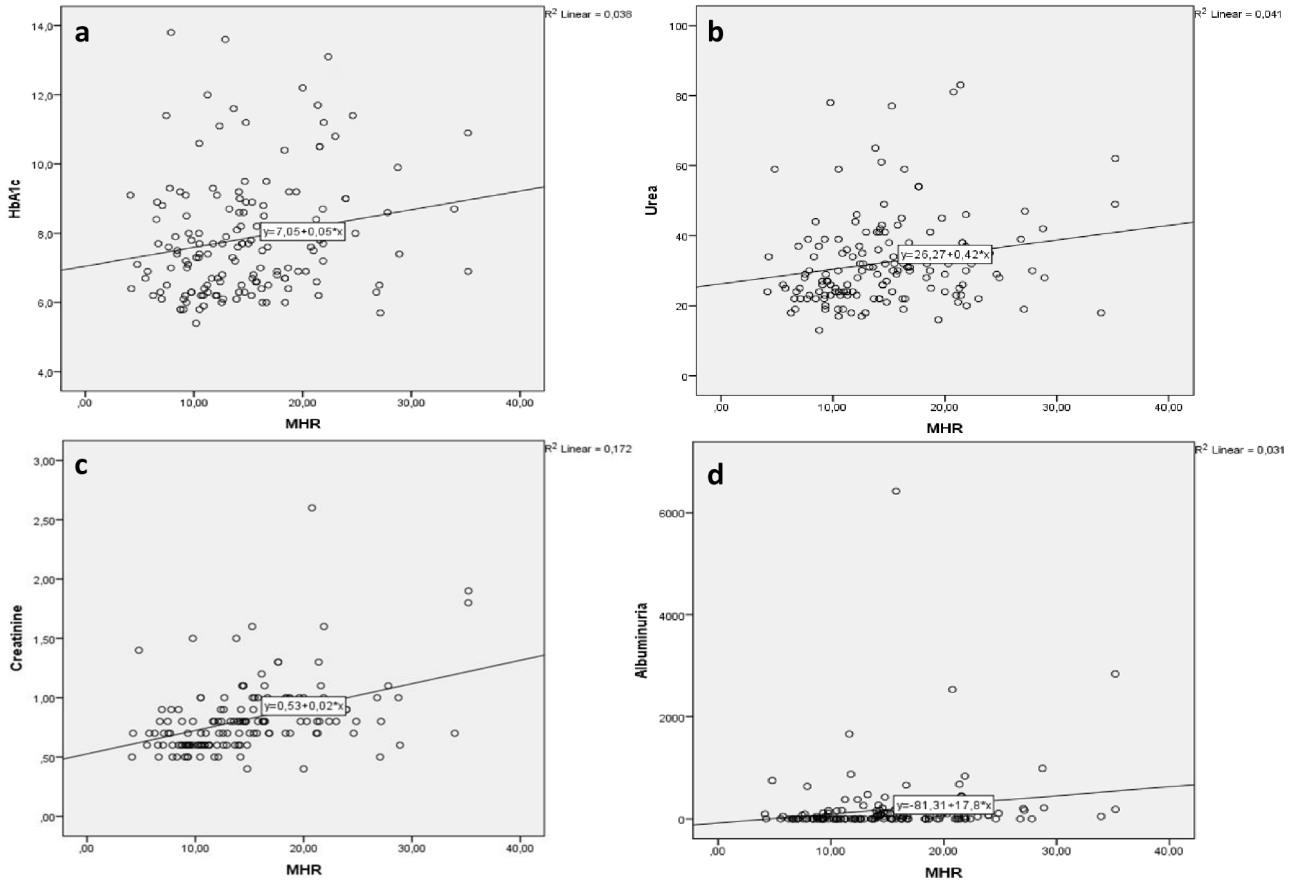

Figure 1. The correlation analyses between MHR and serum level of HbA1c, urea, creatinine, and albuminuria in patients with diabetes mellitus

Table 4. The Linear Regression Analysis of albuminuria and other parameters in patients with diabetic nephropathy

Parameters	Standardized beta	t	p value	95% CI
Step 1				
Age (years)	-0.190	-1.869	0.066	-32.398-1.092
Gender	-0.183	-1.829	0.072	-684.161-30.4
LDL-cholesterol (mg/dL)	0.108	1.137	0.260	-2.265-8.233
Creatinine (mg/dL)	0.286	2.687	0.009	171.741-1170.798
HbA1c (%)	0.013	0.133	0.894	-90.557-103.487
MHR	0.515	5.099	0.001	40.872-93.609
Step 4				
Age (years)	-0.206	-2.085	**0.041**	-33.358- -0.711
Creatinine (mg/dL)	0.272	2.623	**0.011**	151.891-1124.293
MHR	0.512	5.186	**0.001**	41.140-92.650

LDL-cholesterol low density lipoprotein cholesterol, HbA1c hemoglobin A1c, MHR monocyte HDL ratio

Discussion

In the study, these conclusions were reached considering that MHR might be a valuable marker for diabetes regulation and prediction of diabetic nephropathy in diabetic patients. First, patients with diabetic nephropathy have a higher MHR than patients with diabetes but without nephropathy. In patients with diabetic nephropathy, MHR is positively correlated with albuminuria, HbA1c, and serum creatinine, and MHR is an independent predictor of albuminuria with age in this patient group.

Diabetic nephropathy is the most common cause of renal failure. Microalbuminuria is the earliest sign of DN and an indicator of cardiovascular mortality and morbidity in diabetic patients (16). Early diagnosis of albuminuria is essential to prevent the progression of nephropathy. In recent years, the MHR has been used as a new prognostic marker, especially in CVD. Non-alcoholic fatty liver disease, heart failure, and malignant diseases are other patient groups in which the efficacy of MHR has been demonstrated (17-19). In clinical practice, MHR is easily calculated by routine tests, which is often requested and inexpensive, making this index advantageous for predicting some diseases. Our study also showed the usability of MHR both in diabetes regulation and in predicting renal complications of diabetes.

In the study, MHR was higher in patients with diabetic nephropathy than in patients with diabetes but without nephropathy. In different studies, the relationship between micro and macrovascular complications of diabetes, other than nephropathy, and MHR has been shown. Recently, in a study comparing patients with and without diabetic peripheral neuropathy, the frequency of polyneuropathy was higher in patients with high MHR (20) and the effectiveness of MHR in predicting diabetic retinopathy (21). MHR was strongly associated with coronary artery disease in diabetic patients, and MHR is an essential biomarker in predicting coronary artery disease in diabetic patients (22). Increased glycation end products in the pathogenesis of DN cause endothelial and monocyte activation with a proinflammatory effect leading to microvascular and macrovascular complications. Microvascular and macrovascular complications are more common in diabetic patients with high oxidative stress and inflammation. Recent studies have reported that MHR may be an indicator of inflammation and oxidative stress and can be used as an indicator of cardiovascular diseases in particular (23,24). Our study shows that MHR can be an effective marker in predicting renal complications as well as other complications of diabetes.

We found that MHR and albuminuria, HbA1c, and serum creatinine were positively correlated in patients with diabetic nephropathy. In addition, we found that MHR was an independent predictor of albuminuria with aging in patients with diabetic nephropathy. Recent studies have shown an increase in MHR in parallel with decreased GFR in patients with mild renal dysfunction (25.) Karataş et al. found that MHR was positively correlated with urine albumin/creatinine ratio, independent of all other variables (26). Kahraman et al. reported that MHR was positively correlated with 24-hour urinary albumin excretion and negatively correlated with GFR. In this study, similar to our study, MHR was higher in patients with diabetic nephropathy than in diabetic patients without nephropathy (27). Monocytes are inflammatory cells that have essential roles in atherosclerosis with their proinflammatory and prooxidant effects, which we mentioned before (28). Apart from inflammation and oxidative stress, glomerular hemodynamic changes have a role in the pathogenesis of diabetic nephropathy (29). Considering the roles of monocytes and HDL-C in atherosclerosis and related renal hemodynamic changes in addition to inflammation, the relationship between MHR and creatinine, and GFR can be attributed to these existing roles.

In conclusion, it may be possible to predict both the regulation of diabetes and its renal complications with MHR, which is an easily calculated marker with simple laboratory tests in the follow-up of diabetic patients. Therefore, MHR may become a frequently used indicator in the near future.

Conflicts of interest: All authors declare that there is no conflict of interest in this study.

Informed consent: Ethics committee approval was obtained from the institution for the study and written consent was obtained from all patients.

Author Contributions

Conception: H.Ö, İ.B., Data Collection and Processing: K.Z.A, H.Ö., Design: H.Ö,K.Z.A, İ.B., Supervision: İ.B.., Analysis and Interpretation: Y.Ö., F.Y., Literature Review: Y.Ö., F.Y., Writer: H.Ö, I.B., Critical Review: İ.B.

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