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ORIGINAL RESEARCH

Metabolic syndrome as a risk factor for high intraocular pressure: the Korea National Health and Nutrition Examination Survey 2008–2010

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Background: High intraocular pressure (IOP) is well established as the most significant risk factor for both the development and progression of primary open-angle glaucoma. Elevated IOP is more frequently seen in the presence of metabolic disturbances that are associated with the components of metabolic syndrome (MetS). The aim of this study was to investigate the association between ocular hypertension and MetS.

Patients and methods: We examined the relationship between ocular hypertension and MetS in 17,160 Korean adults without glaucoma aged >19 years (7,368 men and 9,792 women) who participated in the 2008–2010 Korea National Health and Nutrition Examination Survey. Multivariate logistic regression analysis was used to assess the relationship between MetS and ocular hypertension, after adjusting for age, body mass index, smoking, alcohol consumption, and regular exercise.

Results: The prevalence of MetS was 35.1% among males and 30.1% among females. The prevalence of ocular hypertension was 1.3% among males with MetS and 0.7% among females with MetS. Participants with MetS had a significantly higher IOP than those without MetS ($P \leq 0.001$), and each component of MetS had a different effect on the IOP. Hypertension was the strongest predictor of an elevated IOP. In multivariate regression analysis, ocular hypertension was significantly associated with MetS ($P=0.027$ for men; $P=0.015$ for women).

Conclusion: There is a statistically significant relationship between MetS and ocular hypertension.

Keywords: intraocular pressure, glaucoma, metabolic syndrome, obesity, hypertension

Introduction

Glaucoma is a progressive optic nerve disease characterized by optic disc cupping and is a significant cause of irreversible blindness worldwide.[1] The early detection and treatment of glaucoma is the key because blindness is irreversible. High intraocular pressure (IOP) is the most significant risk factor for both the development and progression of primary open-angle glaucoma.[2]

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that includes central obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low levels of high-density lipoprotein (HDL) cholesterol.[3] Diabetes mellitus (DM), hypertension, central obesity, body mass index (BMI), age, and metabolic disturbances associated with the components of MetS have been associated with elevated IOPs.[4–7] It is important to identify modifiable glaucoma risk factors to prevent blindness and to optimize the factor-focused management of systemic diseases with glaucoma, such as that has been done in the treatment of cardiovascular diseases.[8] Mitigation of these additional risk factors may help in the prevention and treatment of glaucoma.

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The aim of this study was to investigate the association between MetS and ocular hypertension, taking into consideration the confounding factors, including systemic health parameters. Specifically, we investigated the five key components of MetS in relation to IOP elevation.

Patients and methods

Data source and participants

This study was based on data obtained from the 2008 to 2010 Korean National Health and Nutrition Examination Survey (KNHANES), a cross-sectional and nationally representative survey conducted by the Korea Center for Disease Control and Prevention and approved by its institutional review board. The KNHANES used a multistage stratified probability-clustered sampling method and a weighting scheme that allowed for the estimation of health statistics representative of noninstitutionalized civilians who resided in Korea. Additional details regarding the survey design and methods have been provided elsewhere.[9] All participants in the KNHANES provided written informed consent prior to commencement of the study.

Our study subjects were Koreans who participated in the 2008–2010 KNHANES. We selected 21,811 subjects who were ≥19 years of age. Among these, we excluded 2,750 subjects who had not undergone thorough ophthalmic examinations, 1,107 subjects with missing data for MetS components, 53 subjects with glaucoma, 326 subjects with a history of ophthalmic surgery, and 413 subjects who had other missing data. Thus, a total of 17,160 subjects (7,368 men and 9,792 women) were included in the analysis. The study protocol was approved by the institutional review board of the Pusan National University Hospital, Pusan, Korea (2015-11-026).

Data collection

The KNHANES consisted of a health interview and a health examination including an ophthalmological interview and examination. All KNHANES interviews and examinations were performed by trained staff according to standardized procedures.

Self-reported questionnaires were administered to the participants to collect data regarding demographic characteristics, smoking status, alcohol consumption, daily exercise level, sleep duration, and history of chronic disease including hypertension, dyslipidemia, and DM. Subjects reported their smoking status by self-administered questionnaires and were divided into two groups: 1) current smokers or 2) non- or ex-smokers, according to their self-reported smoking behavior. A current cigarette smoker was defined as an adult who had smoked at least 100 cigarettes in their lifetime and currently smoked cigarettes. We converted the amount of alcohol consumed per drinking day and the frequency of days drinking in the past month into the mean daily alcohol consumption (g pure alcohol/day). Using the WHO classification,[10] heavy drinkers were defined as >20 g pure alcohol/day for women and >40 g pure alcohol/day for men. Physical activity was defined based on the subjects' responses to a modified version of the International Physical Activity Questionnaire.[11] Subjects were classified as regular exercisers if they performed ≥30 minutes of moderate-intensity physical activity at least 5 days/week, ≥20 minutes of vigorous-intensity physical activity at least 3 days/week, or ≥30 minutes of walking at least 5 days/week, during the previous week.

All anthropometric measurements were obtained by a trained examiner. Waist circumference (WC) was measured at the end of a normal expiration with the arms relaxed at the sides. WC was measured at the mid-point between the margin of the lowest palpable rib and the top of the iliac crest. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with participants wearing light indoor clothing without shoes. BMI was calculated as the ratio of weight (kg) to height squared (m^2). Blood pressure measurements were obtained from the right arm using a standard mercury sphygmomanometer (Baumanometer, Copiague, NY, USA). SBP and DBP were measured three times at 5, 10, and 15 minutes and an average was calculated from the second and third measurements. Ophthalmological examinations were performed by a trained ophthalmologist or ophthalmology resident. IOP was measured three times in both eyes using a slit-lamp mounted Goldmann application tonometer (Haag-Streit model BQ-900; Haag-Streit AG, Koeniz, Switzerland). The results were averaged for analysis.

Venous blood samples were obtained after an 8-hour minimum overnight fast. Fasting plasma glucose, triglyceride, and HDL cholesterol levels were measured using an ADVIA1650 autoanalyzer (Siemens Medical Solutions Diagnostics, Erlangen, Germany). Insulin concentrations were measured with an immunoradiometric assay (INS-IRMA; BioSource, Nivelles, Belgium) using the 1470 WIZARD automatic gamma counter (PerkinElmer, Turku, Finland) for the measurement of serum insulin levels. The assay coefficient of variation was <5% for insulin. We used the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) to calculate insulin resistance (IR) ([fasting plasma insulin (μIU/mL) × glucose (mg/dL)]/22.5). The quantitative insulin-sensitivity check index (QUICKI) value was calculated using the following formula: (1/[log fasting plasma insulin (μIU/mL) + log fasting plasma glucose (mg/dL)]). Individuals with ≥2.34 HOMA-IR were defined as

insulin resistant, and those with ≥0.34 QUICKI were defined as insulin sensitive (IS).[12]

We used the Korean-specific cutoffs of the revised National Cholesterol Education Program-Adult Treatment Panel III to assess for abdominal obesity.[13] MetS was defined as any three of the following five metabolic components: 1) WC ≥90 cm in men and ≥85 cm in women, 2) serum HDL-cholesterol level <40 mg/dL in men and <50 mg/dL in women, 3) serum triglyceride level ≥150 mg/dL or treatment of dyslipidemia, 4) blood pressure ≥130/85 mmHg or treatment of hypertension, and 5) fasting glucose level ≥100 mg/dL or treatment of type 2 diabetes.

Statistical analyses

In KNHANES, the sampling results were weighted to allow for nationally representative prevalence estimates of the Korean population. The weights were calculated by accounting for the complex survey design, survey non-response, and post-stratification. The statistical analysis accounted for the complex sampling design of the KNHANES to minimize selection errors. The estimates reported in this study were obtained with consideration for the primary sampling unit, stratification variables, and sampling weights. The analysis was adjusted for survey year to minimize the variations between survey years.[14,15] Descriptive data were expressed as the mean value (standard error) or number (%). Analysis of continuous variables was performed using the chi-squared test, and categorical variables were analyzed using the *t*-test of general linear model; and presented as percentages and standard errors. The clinical characteristics of subjects were compared according to gender and clinical diagnosis of MetS. The mean IOPs were compared between different MetS components, according to gender, among participants with MetS. We grouped the patients into different categories of MetS components and compared the mean IOPs between the groups with elevated parameters and those without. For example, to determine the correlation between obesity and IOP, differences in IOP between the obese and non-obese groups were analyzed. Obesity was defined as BMI 25 or higher. Simple and multiple logistic regression analyses were applied to evaluate the association between MetS and ocular hypertension (IOP >21 mmHg). Calculations were performed after adjusting for age, BMI, smoking, heavy drinking, and regular exercise. All analyses were performed using SPSS (Version 18.0; SPSS Inc., Chicago, IL, USA) and *P*-values <0.05 were considered statistically significant. All statistical tests were two-tailed.

Results

The clinical characteristics of the study populations are summarized in Table 1. There were 1,915 men and 2,282 women

Table 1 Clinical characteristics of study populations according to the clinical diagnosis of MetS

	Men			Women		
	without MetS	With MetS	*P*-value	Without MetS	With MetS	*P*-value
	(n=5,453)	(n=1,915)		(n=7,510)	(n=2,282)	
Age (years)	37.27±0.21	54.86±0.29	<0.001	42.57±0.28	59.34±0.42	<0.001
BMI (kg/m^2)	22.13±0.4	26.27±0.07	<0.001	22.4±0.15	26.23±0.11	<0.001
WC (cm)	75.28±0.13	89.69±0.18	<0.001	75.26±0.17	87.91±0.28	<0.001
SBP (mmHg)	111±0.18	128.51±0.31	<0.001	109.89±0.27	130.64±0.46	<0.001
DBP (mmHg)	71.98±0.14	80.98±0.20	<0.001	70.79±0.18	79.22±0.27	<0.001
FBS (mg/dL)	91.95±0.17	111.89±0.52	<0.001	90.80±0.20	111.11±0.83	<0.001
HDL (mg/dL)	55.06±0.14	44.37±0.20	<0.001	57.93±0.19	46.14±0.28	<0.001
TG (mg/dL)	105.44±0.85	220.04±3.25	<0.001	91.28±0.78	187.08±3.01	<0.001
Mean IOP (mmHg)	13.86±0.05	14.43±0.07	<0.001	13.68±0.06	14.29±0.08	<0.001
Left IOP (mmHg)	13.86±0.05	14.44±0.07	<0.001	13.67±0.06	14.32±0.09	<0.001
Right IOP (mmHg)	13.86±0.05	14.41±0.07	<0.001	13.69±0.06	14.27±0.09	<0.001
Ocular hypertension	28 (0.5)	21 (1.3)	0.012	14 (0.2)	18 (0.7)	0.016
HOMA-IR ≥ 2.34	1,504 (30.4)	1,276 (67.9)	<0.001	1,869 (27.8)	1,539 (70.4)	<0.001
QUICKI ≤ 0.33	1,059 (21.2)	1,073 (56.5)	<0.001	1,232 (18.2)	1,293 (59.9)	<0.001
Heavy drinkers (%)	3,729 (74.0)	1,293 (74.2)	0.001	2,373 (36.0)	418 (22.1)	<0.001
Current smoking (%)	2,350 (52.7)	739 (53.5)	<0.001	442 (6.9)	107 (5.7)	0.049
Regular exercise	3,140 (58.2)	1,044 (53.8)	0.007	3,860 (52.2)	1,146 (50.0)	0.18
Adequate sleep duration	3,173 (58.9)	1,137 (57.8)	0.438	4,587 (52.4)	1,212 (53.2)	<0.001

Notes: Data are presented as mean ± standard error or unweighted number (%). The definition of ocular hypertension was a mean IOP >21 mmHg.
Abbreviations: BMI, body mass index; FBS, fasting blood sugar; HDL, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IOP, intraocular pressure; MetS, metabolic syndrome; QUICKI, quantitative insulin-sensitivity check index; TG, triglycerides; WC, waist circumference.

with MetS included in the study. The mean age was higher in men and women with MetS than healthy subjects: 54.86 vs 37.27 years in men and 59.34 vs 42.57 years in women. The subjects with MetS had significantly higher IOP levels than those without MetS. The mean IOP was 13.86 (±0.05) mmHg in men without MetS, and 14.33 (±0.07) mmHg in men with MetS. Similarly, in females, the mean IOP was 13.68 (±0.06) mmHg in women without MetS and 14.29 (±0.08) mmHg in women with MetS. The prevalence of ocular hypertension was higher in the MetS group in both men and women: 1.3% vs 0.5% in men, and 0.7% vs 0.2% in women. The subjects with MetS had a significantly higher BMI, WC, SBP, triglycerides (TG) level, and fasting blood sugar levels than those without MetS in both sexes. The average sleep duration was significantly longer in subjects without MetS than in subjects with MetS in both men and women. There was no consistent statistically significant difference in smoking, regular exercise, or occupation in either sex. A comparison of the mean values of IOP according to different metabolic components in the MetS subjects showed that both men and women with high blood pressure and elevated fasting glucose levels had significantly higher IOP levels when compared to subjects without these metabolic components ($P<0.05$, respectively) (Table 2). No correlation was found between abdominal obesity and an elevation of IOP.

Table 3 shows a comparison of the mean values of IOP according to subgroups. IOP was significantly higher in the obese group, regardless of the presence or absence of MetS in men.

The subjects with high blood pressure had significantly higher IOP levels than those without hypertension in both men and women. Men with IR and obesity had significantly higher IOP levels regardless of the diagnosis of MetS. However, women with IR and obesity had significantly higher IOP levels without MetS. Table 4 shows the results of the logistic regression analyses assessing the relationship of MetS with ocular hypertension.

The univariate logistic regression analysis between ocular hypertension and MetS indicated that age, BMI, high blood pressure, elevated fasting glucose levels, and elevated TG levels showed a significantly positive association with ocular hypertension in men. However, elevated blood glucose was the only variable significantly associated with ocular hypertension in women ($P<0.05$). In the final multiple logistic regression model (Table 5), the odds ratios (ORs) for ocular hypertension were 2.111 (95% CI, 1.090–4.088) and 2.784 (95% CI 1.221–6.347), respectively, in men and women, after adjustment for age (model 1). After adjusting for age and BMI (model 2), the ORs in men and women were 1.697 (95% CI 0.803–3.586) and 1.066 (95% CI 0.839–1.354), respectively. After adjusting for age, BMI, smoking, heavy drinking, regular exercise, and adequate sleep duration (model 3), the ORs for ocular hypertension in men were 1.685 (95% CI 0.718–3.956) and 2.829 (95% CI 0.933–8.579) in women.

Discussion

In this cross-sectional study, after adjusting for age, we found a positive association between IOP and MetS in Korean

Table 2 Comparison of the mean values of intraocular pressure according to metabolic components in MetS subjects

	Men			Women		
	n	Mean ± SE	*P*-value	n	Mean ± SE	*P*-value
Abdominal obesity						
No	685	14.19±0.08	0.125	707	14.12±0.08	0.596
Yes	1,228	14.34±0.1		1,563	14.07±0.07	
High blood pressure						
No	401	14.09±0.08	<0.001	473	13.9±0.07	0.001
Yes	1,512	14.43±0.09		1,808	14.19±0.08	
Elevated fasting glucose						
No	506	14.06±0.08	<0.001	806	13.83±0.07	<0.001
Yes	1,403	14.43±0.1		1,456	14.26±0.08	
Low HDL cholesterol						
No	980	14.43±0.07	0.001	604	14.15±0.07	0.96
Yes	916	14.1±0.11		1,642	14.04±0.08	
Elevated triglycerides						
No	317	14.06±0.09	<0.001	581	13.97±0.07	0.062
Yes	1,588	14.45±0.09		1,685	14.12±0.08	

Note: The MetS components were defined as: abdominal obesity (waist circumference of men ≥90 cm, women ≥85 cm); high blood pressure (systolic ≥130 mmHg, diastolic ≥85 mmHg); elevated fasting glucose (≥100 mg/dL); low HDL cholesterol (HDL cholesterol of men <40 mg/dL, women <50 mg/dL); and elevated triglycerides (≥150 mg/dL).
Abbreviations: HDL, high-density lipoprotein; MetS, metabolic syndrome.

Table 3 Comparison of mean values of IOP according to subgroups

	Men				Women			
	IOP without MetS	***P*-value**	**IOP with MetS**	***P*-value**	**IOP without MetS**	***P*-value**	**IOP with MetS**	***P*-value**
SBP (mmHg)								
≤139	14.04±0.07	0.613	14.48±0.11	0.139	13.66±0.06	0.01	14.19±0.1	0.04
≥140	14.14±0.20		14.80±0.20		14.04±0.15		14.5±0.13	
DBP (mmHg)								
≤89	14.02±0.07	0.01	14.51±0.11	0.352	13.67±13.97	0.128	14.23±0.09	0.023
≥90	14.46±0.18		14.68±0.18		13.98±0.2		14.65±0.18	
HOMA-IR								
≤2.33	13.94±0.07	0.002	14.29±0.1	0.013	13.61±0.07	0.001	14.28±0.13	0.875
≥2.34	14.29±0.11		14.69±0.1		13.89±0.09		14.31±0.1	
QUICKI								
≥0.34	13.89±0.07	<0.001	14.21±0.17	0.007	13.61±0.07	<0.001	14.33±0.15	0.943
≤0.33	14.35±0.13		14.74±0.12		14.02±0.1		14.34±0.11	
BMI (kg/m^2)								
≤24.9	13.98±0.07	0.04	14.2±0.15	0.001	13.64±0.06	0.027	14.33±0.13	0.651
≥25	14.20±0.10		14.72±0.72		13.85±0.1		14.27±0.1	

Abbreviations: BMI, body mass index; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IOP, intraocular pressure; MetS, metabolic syndrome; QUICKI, quantitative insulin-sensitivity check index.

Table 4 Univariate logistic regression analyses showing the association of MetS to ocular hypertension in all subjects

	Men		Women	
Variables	**ORs**	**95% CI**	**ORs**	**95% CI**
Age (10 years)	1.183	1.041–1.344	1.206	0.942–1.543
BMI (kg/m^2)	1.093	1.021–1.169	1.068	0.993–1.149
Abdominal obesity	1.788	0.739–4.324	0.972	0.394–2.394
High blood pressure	2.989	1.533–5.828	1.991	0.825–4.805
Elevated fasting glucose	2.162	1.122–4.167	2.611	1.068–6.385
Elevated triglycerides	2.339	1.116–4.905	1.13	0.465–2.750
Low HDL cholesterol	0.911	0.408–2.033	1.998	0.824–4.842
High HOMA-IR	1.811	0.945–1.080	2.326	0.829–6.525
Low QUICKI	2.133	0.933–4.875	1.931	0.656–5.679
MetS	2.375	1.238–4.555	3.089	1.293–7.382
Heavy drinking	1.729	0.618–4.839	0.772	0.275–2.169
Smoking	1.939	0.609–6.174	0.755	0.135–4.221
Regular exercise	1.063	0.548–2.065	1.418	0.542–3.706
Adequate sleep duration	1.25	0.594–2.630	0.613	0.251–1.494

Note: The components of MetS were defined as: abdominal obesity (waist circumference of men ≥90 cm, women ≥85 cm); high blood pressure (systolic ≥130 mmHg, diastolic ≥85 mmHg); elevated fasting glucose (≥10 mg/dL); low HDL cholesterol (HDL cholesterol of men <40 mg/dL, women <50 mg/dL); and elevated triglycerides (≥150 mg/dL); high HOMA-IR (≥2.34); low QUICKI (≤0.33).

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; MetS, metabolic syndrome; QUICKI, quantitative insulin-sensitivity check index.

Table 5 Multiple logistic regression analyses showing the association of metabolic syndrome to ocular hypertension

	Men		Women	
	ORs	**95% CI**	**ORs**	**95% CI**
Model 1	2.111	1.090–4.088	2.784	1.221–6.347
Model 2	1.697	0.803–3.586	1.066	0.839–1.354
Model 3	1.685	0.718–3.956	2.829	0.933–8.579

Notes: Model 1. Adjusted for age. Model 2. Adjusted for age and BMI. Model 3. Adjusted for age, BMI, smoking, heavy drinking, regular exercise, and adequate sleep duration.

Abbreviation: BMI, body mass index.

adults without glaucoma. Previous studies have found that an elevated IOP was associated with elevated blood pressure,[16,17] elevated blood glucose levels,[18] and with obesity.[4] In this study, we found significant differences in IOP according to the degree of IR.

In the current study, we found that subjects with a MetS component are prone to a greater elevation in IOP than those without MetS components. This result is supported by the finding that IOP was significantly correlated with the

presence of MetS. Among subjects with MetS, high blood pressure and elevated fasting blood glucose levels had significant effects on IOP. Most previous studies have consistently reported a significant influence of blood pressure on IOP.[19,20] High blood pressure has been considered to elevate IOP by not only increasing ciliary artery pressure and increasing the production of aqueous humor but also through an increase in serum corticosteroids and sympathetic tone.[21] High blood pressure was associated with increase in IOP in men. Hypertension is a risk factor for cardiovascular disease and is associated with increased IOP. Assessing the IOP among asymptomatic patients with hypertension as part of primary care may be a simple but effective strategy to ensure earlier detection of glaucoma.

The association between an elevated fasting blood glucose and ocular hypertension was significant in both men and women in this study. However, the mechanism of how hyperglycemia affects IOP is not fully understood. Possible reasons for this association are an increased osmotic gradient induced by an elevated blood glucose, with a consequent fluid shift into the intraocular space, and autonomic dysfunction.[22] Our analyses used two indices of IR: the HOMA-IR and the QUICKI. The HOMA-IR is a widely used index of IR that can be calculated from fasting insulin and glucose levels.[23] Many previous studies have reported that an increased fasting glucose level is a risk factor for an elevated IOP; therefore, we used a second IS index, the QUICKI, that is derived from the inverse sum of the logarithms of the fasting insulin and fasting glucose levels. The QUICKI correlates well with glucose clamp studies (r=0.78) and is useful for measuring IS, which is the inverse of IR.[24] Regardless of the index chosen, the IOP was significantly higher in subjects with a severe degree of IR, with the exception of that seen in women with MetS. Also, in women with MetS, there was no association of IOP with BMI.

Our study has several limitations. First, our study used a cross-sectional design, which did not clarify the effect of causal relationships; therefore, additional prospective studies are needed to establish a cause and effect relationship between ocular hypertension and MetS. Second, we could not fully exclude the effects of recall bias since our study included lifestyle factor data based on a self-reported questionnaire survey. Lastly, we did not assess the levels of endogenous cortisol and steroid hormones that could possibly cause morphological changes in the trabecular meshwork and the intra- or extraocular tissues, affecting the IOP balance. Also, we did not assess bone mass, which could affect IOP, especially since the concentration of osteocalcin is associated with IR.

On the other hand, a major strength of our study was the use of data from a nationally representative sample of the adult population of Korea. Another strength was the use of a standardized manual for conducting clinical assessments, anthropometric measurements, and biochemical examinations by trained examiners and interviewers.

The prevalence of MetS is rapidly increasing worldwide because of sedentary lifestyles and unhealthy diets. This study showed a significant correlation between IOP and MetS. Future studies should be carried out to investigate the following points: 1) the therapeutic benefits of lifestyle interventions for the prevention and treatment of MetS and the effect on lowering IOP, and 2) prospective studies analyzing the influence of central retinal thickness on future IOP. In summary, we have shown that individuals with MetS are more likely to have an elevated IOP. This study also showed that four of the five components of MetS (elevated fasting plasma glucose, elevated blood pressure, elevated triglyceride, and low HDL) were associated with higher IOPs.

Conclusion

In this cross-sectional study, ocular hypertension was associated with MetS in Korean adults. These findings also suggest that IOP changes may be associated with MetS, and particularly, IR.

Disclosure

The authors report no conflicts of interest in this work.

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