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Epidemiology

Diagnostic performance of retinal digital photography for diabetic retinopathy screening in primary care

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Abstract

Introduction. We must study alternatives to structure an effective diabetic retinopathy screening program for Brazilian public health system.

Objectives. Evaluate the diagnostic performance of retinal digital photography for diabetic retinopathy screening in primary care, accuracy of the family physician in diabetic retinopathy identification compared to the ophthalmologist, and the need for dilation.

Methodology. In a primary care service were performed retinal photographs with non-mydriatic Retinal Camera in 219 type 2 diabetic patients with and without medication mydriasis. We evaluated the performance of the diagnostic of the photos graded by three family physicians with training compared to two ophthalmologists (gold standard), and explore related factors with the need for mydriasis pharmacologically.

Results. The prevalence of diabetic retinopathy and proliferative diabetic retinopathy was 19.2% and 1.5%, respectively. The sensitivity of family physicians to evaluate diabetic retinopathy averaged 82.9% (66.7–94.8%); specificity, 92% (90.2–93.3%); the accuracy, 90.3% (88.2–93%) and positive predictive value, 71.2% (68–75.5%). The agreement calculated using the kappa adjusted coefficient was from 0.74 to 0.8 for retinopathy and 0.88 to 0.92 for macular edema. Without drug mydriasis the photos were unreadable by 14.8%, when using mydriatic collyrium this number decreased to 8.7% (McNemar test, $P < 0.005$). Patients with more than 65 years old has more readability after drug mydriasis (McNemar test, $P = 0.011$).

Conclusion. Trained family physician reached a good performance for evaluation of retinography for diabetic retinopathy. There was improvement in readability with pupil dilation in older patients.

Key words: Diabetes / insulin resistance, family health, ophthalmology / visual impairment, prevention, screening.

Introduction

Diabetic retinopathy (DR) is the leading cause of new-onset blindness in adults aged 20–74 years (1). Its prevalence is related to diabetes duration, glycemic control and hypertension (2)The prevalence of DR in patients with type 2 diabetes ranges from 12.3% to 39%; in studies conducted in primary-care settings, rates around 20% are common. The prevalence of proliferative DR (PDR) ranges from 0.3% to 10.6%, most often representing 2% of all DR cases (2, 3).

The gold standard for the diagnosis and classification of retinopathy is seven-standard-field stereoscopic colour fundus photography supplemented by a comprehensive dilated eye examination with slit-lamp examination of the retina, to allow accurate assessment of retinal thickness (4). This technique is costly and requires specialized equipment and professionals; in most health systems, it is preceded by screening. Retinal photography (with or without mydriasis) assessed by an experienced ophthalmologist is the most effective method for large-scale detection of DR, and, when combined with telemedicine capabilities, enables remote diagnosis (5, 6). In some settings, family physicians (FP) have been trained to screen for DR and referring for evaluation by ophthalmologists only those patients who have some degree of DR, thus improving access to care by affected individuals (5). One of the main motivations for DR screening is the established efficacy of laser photocoagulation in preventing visual loss (4, 7).

Brazil has approximately one ophthalmologist for every 10 600 population. Although this figure exceeds the World Health Organization-recommended ratio of 1:17 000, the distribution of these professionals across the country is very uneven, with 57% of ophthalmologists practicing in the Southeast region of Brazil and many working outside the public health system (8). Within this context, the interval between diagnosis of diabetes and first eye examination ranges from 7 to 19.5 years (mean, 13.3 ± 5.1 years) for patients with type 1 diabetes and 3 months to 18 years (mean, 5.2 ± 4.81 years) for those with type 2 diabetes, even in the best-served regions (9).

In this study, our goal was to assess the ability of trained FPs to screen for DR. This shift in work process could improve care in the Brazilian health system and allow faster referral of at-risk cases.

Objectives

To evaluate the diagnostic performance of digital retinal photography for DR screening, performed by FPs, as compared with evaluation of the same photographs by experienced ophthalmologists (gold standard), and evaluate which factors influence the quality of photos obtained, including the need for pharmacologic mydriasis.

Methodology

This study was conducted in two phases. The first phase consisted of training of FPs to evaluate their patients' retinal photographs for DR, while the second phase consisted of a performance evaluation of FPs thus trained in the identification of DR as compared to the gold standard, descriptive analysis of the study population, and evaluation of the need for pupillary dilation.

Training of family physicians

FPs were provided a 15-hour course consisting of 7 hours of distance learning, with tutoring for problem solving and 8 hours of face-to-face, small-groups training in theoretical and practical classes with an ophthalmologist. The topics addressed were the pathophysiology of DR and its classifications, basic notions of treatment, referral, how to capture images with the retinal camera (with and without pharmacologic mydriasis), identification of artefacts, and other diseases that often affect the retina. The student evaluation consisted of a practical online test.

Performance of family physicians to identify diabetic retinopathy lesions

Patient sample

The study sample consisted of adult patients with type 2 diabetes registered at a primary care centre (Basic Health Unit) in Southern Brazil. The sample was recruited using a convenience strategy from the pool of patients enrolled in the diabetes program of the health unit. Patients with a previous diagnosis of cataract were excluded because this pathology hinders correct visualization of the retina. Patients with type 1 diabetes were not included because of the low prevalence in primary care.

Clinical data

The variables of interest for descriptive analysis were: sex, age, self-reported skin colour (white or non-white), diabetes duration (in years), glycated haemoglobin (by high-performance liquid chromatography), presence of hypertension, nephropathy and use of anti-diabetic agents. Patients with systolic blood pressure below 140 mmHg and diastolic below 90 mmHg and no history of hypertension were classified as normotensive.

Presence of hypertension was defined by diagnosis of hypertension in the medical record. Those with a history of hypertension, current antihypertensive therapy and normal blood pressure, were classified as having controlled hypertension, and those with blood pressure values above these as having uncontrolled hypertension. Evaluation of nephropathy consisted of 24-hour urinary albumin testing (by immunoturbidimetry), with values defined as follows: <30 mg, normal; 30–299 mg, microalbuminuria; ≥300 mg, macroalbuminuria. Chronic kidney disease was defined by a glomerular filtration rate <60 ml/min/1.73m^2 (CKD-EPI equation) or a serum creatinine level ≥2 mg/dl. The parameters used for hypertension and nephropathy were based on the standards of medical care in diabetes published by the American Diabetes Association, Diabetes Care, 2015.

Ophthalmologic examination and development of the gold standard

DR was classified according to the International Clinical Classification System for Diabetic Retinopathy and Diabetic Macular Edema (10), which categorizes DR as absent (no apparent retinopathy); mild nonproliferative (characterized by microaneurysms only); moderate nonproliferative (microaneurysms, exudates and haemorrhages); severe nonproliferative (more than 20 haemorrhages on each of the four quadrants or venous beading in two or more quadrants, or prominent intra-retinal microvascular abnormalities, but no signs of proliferative retinopathy); and proliferative, with neovascularization or vitreous haemorrhage or pre-retinal haemorrhage. Diabetic macular edema (DME) is classified as absent, moderate, or severe according to the distance from the macula and the need for referral for further evaluation by an ophthalmologist.

Ophthalmologic examination was performed through digital retinal photography of two fields in each eye. The FP captured the

photographs with a Canon CR-2 non-mydriatic retinal camera, with and without pharmacologic mydriasis. Participants were sent to a dark room and, after at least 3 minutes, two photos of each eye were taken, one centred at the macula and another at the optic disc. After the first photograph, pupillary dilation was performed if possible, using a single drop of anaesthetic (proparacaine 5 mg/ml) followed by a drop of 0.5% tropicamide and 10% phenylephrine in each eye, reapplied after 10 minutes. After 15 minutes, the photographs were repeated.

The photographs were evaluated by three FPs and two ophthalmologists. For evaluation, the photographs were numbered randomly, without any information about clinical data or pharmacologic mydriasis, by a researcher not involved in image analysis. Each evaluation included two photographs of each eye. The photographs obtained with dilation were assessed independently of those captured without dilation. All photographs were stored and made available in an online digital repository for evaluation. All professionals completed a standardized report for each eye, regarding photo readability (characterized as unreadable, questionable or readable), presence and severity of retinopathy (classified as absent, mild nonproliferative, moderate nonproliferative, severe nonproliferative or proliferative), presence and severity of DME (classified as absent, mild, moderate or severe), and case disposition (annual review, referral to ophthalmologist for RD or DME, or referral for other reasons).

The gold standard was constructed on the basis of evaluation by two ophthalmologists. When there was disagreement between the ophthalmologists, the case was discussed to establish a consensus. If such consensus was not possible, the corresponding photographs and assessments previously performed by the ophthalmologists were sent to a third professional (retina specialist), whose evaluation was then considered the gold standard.

Statistical aspects

Descriptive statistics were used to characterize the clinical and laboratory characteristics of the study sample: means and standard deviations for normally distributed variables and medians and quartiles for nonparametric variables. The normality of these variables was evaluated by histogram graph, q-q plot and Shapiro-Wilk e Kolmogorov-Smirnov tests with SPSS 20.0.

The sample size for calculation of agreement between observers, estimating a kappa coefficient >0.8 (denoting very good agreement) and a 20% prevalence of DR, was established as 165 patients. Analysis of agreement using kappa coefficients adjusted for prevalence were conducted to evaluate the diagnostic performance of FPs. Sample size and adjusted kappa calculations were performed in the WINPEPI software environment, while additional statistical analyses were conducted in SPSS 20.0. Sensitivity, specificity, positive predictive value and accuracy of FPs were calculated by comparison to the gold standard described above. Positive and negative agreement between FP and gold standard were calculate

To evaluate the effect of pharmacologic mydriasis on the quality and readability of 366 digital fundus photographs (183 right eyes with and without dilatation), we used descriptive statistics. The association between patient characteristics and readability of fundus photographs was evaluated using the McNemar test.

Results

We evaluated 219 patients with type 2 diabetes, whose characteristics are described in Table 1. The mean age was 64.9 ± 11.0 years, and 131 were women (59.8%). The sample was overwhelmingly white (89%) and hypertensive (90.4%); 20.5% of participants had nephropathy. Glycated haemoglobin levels were <6.5% in 36.4% of participants, and hypertension was controlled in 64% of those with this condition. The overall prevalence of DR according to the gold standard was 19.2% (1.5% PDR). Macular edema was present in 5% of the sample, being severe in 1% of cases (Table 2).

All FPs completed the training course before starting evaluation of fundus photographs.

The results of the ophthalmologists' evaluation, when in agreement, were considered the gold standard. There was no agreement in classification of 64 DR cases and 35 DME cases. To construct a gold standard in these situations, ophthalmologists discussed the reports in person to obtain a consensus. In eight cases, the ophthalmologists failed to reach a consensus, and the tiebreaker was provided by a retina specialist who had access to the fundus photographs and to the ophthalmologists' evaluations.

The average sensitivity of FPs to evaluate DR was 82.9% (66.7–94.8%); specificity, 92% (90.2–93.3%); accuracy, 90.3% (88.2–93%); and positive predictive value, 71.2% (68–75.5%), while for macular edema, the average sensitivity was 30% (10–70%), specificity, 96.6% (95.1–98.4%); accuracy, 93.1% (90.7–94.8%); and positive predictive value, 28.3% (10–50%) (Table 3).

Agreement between the gold standard and the FPs, calculated using the prevalence-adjusted kappa coefficient, ranged from 0.74 to 0.8 for DR and 0.88 to 0.92 for DME. Percent agreement ranged from 79.3% to 83.7% for DR and 90.8% to 93.9% for DME (Table 4).

Of the 366 photographs included in evaluation of readability, 43 (11.7%) were unreadable, 73 (19.9%) were questionable, and 250 (68.3%) were readable. Regarding quality, 44 (12%) were considered poor, 66 (18%) fair, and 256 (69.9%) were classified as good.

The effect of pupillary dilation on the quality of retinal photographs is described in Table 5. Analysis of factors associated with readability identified that patients with unreadable images had a median age of 72.5 ± 9.8 years, while those with readable and questionable images were, on average, aged 62.6 ± 11.3 and 64.3 ± 9.8 years, respectively. When we stratified the sample by age, we identified 89 patients (48.6%) under 65 years and 94 patients (51.4%) aged 65 or older. In the older group, pharmacologic mydriasis was associated with improved image readability (McNemar test, $P = 0.008$), but not among the younger group. (McNemar test, $P = 0.579$) (Table 5). The other factors considered—diabetes duration, presence of hypertension, presence of nephropathy—did not influence readability of fundus photographs.

With screening, 68.5% and 60.6% of patients (per gold-standard and FP evaluation, respectively) avoided referral to an ophthalmologist. Percent agreement of referrals was 69.4% between the gold standard and two FPs and 74.4% between the gold standard and the third FP. All cases of proliferative DR were referred by FPs. One FP referred all cases of moderate and severe DME, one physician failed to refer one case out of six, and another referred only two cases.

Discussion

We evaluated the performance of a process of FP-led and FP-managed DR screening carried out in a primary-care setting. One systematic review that evaluated the effectiveness of screening and monitoring for DR suggested that 80% sensitivity would be acceptable for DR screening programs (11). In our study, the sensitivity of FPs for DR evaluation ranged from 66.7% to 94.8%, with a reasonable average of 82.9%. Specificity was good, ranging from 90.2% to 93.3%

Table 1. Clinical and laboratory characteristics of the sample by convenience of patients with type 2 diabetes registered at a primary care centre in Southern Brazil

Characteristic	Overall	Retinopathy absent	Proliferative retinopathy
N (%)	219 (100%)	164 (74.9%)	3 (1.37%)
Age in years, mean ± SD	64.89 ± 11.01	64.09 ± 10.5	68.33 ± 11.93
Male, n (%)	88 (40.2%)	67 (40.9%)	1 (33.3%)
White, n (%)	195 (89.0%)	148 (90.2%)	2 (66.7%)
Diabetes duration in years, median (IQR)*	6 (3–14)	5 (3–10)	19 (14–20)
Hemoglobin A1C %, median (IQR)**	7.0 (6.2–8.5)	6.8 (6.1–8.0)	10.1 (8.3–15.3)
Hemoglobin A1C % ≥ 6.5%, *n* (%)**	76 (36.4%)	65 (41.1%)	—
Hemoglobin A1C % < 8%, *n* (%)**	71 (34%)	46 (27.2%)	3 (100%)
Treatment***, *n* (%)			
Diet only	12 (5.7%)	11 (6.9%)	—
Oral antidiabetics	141 (66.5%)	114 (71.3%)	2 (66.7%)
Insulin	59 (27.8%)	35 (21.9%)	1 (33.3%)
Nephropathy*, *n* (%)[a]			
Absent	163 (79.5%)	126 (81.8%)	1 (33.3%)
Microalbuminuria	24 (11.7%)	18 (11.7%)	1 (33.3%)
Macroalbuminuria	2 (1.0%)	1 (0.6%)	—
CKD/azotemia	16 (7.8%)	9 (5.8%)	1 (33.3%)
Blood pressure status, *n* (%)[b]			
Normotensive	21 (9.6%)	18 (11%)	—
Controlled hypertension	140 (63.9%)	105 (64%)	—
Uncontrolled hypertension	58 (26.5%)	41 (25%)	3 (100%)

IQR, interval interquartile; CKD, chronic kidney disease.

[a]Evaluation of nephropathy consisted of 24-hour urinary albumin testing (by immunoturbidimetry), with values defined as follows: <30 mg, normal; 30–299 mg, microalbuminuria; >300 mg, macroalbuminuria.

[b]Presence of hypertension was defined by diagnosis of hypertension in the medical record. Normal blood pressure and controlled hypertension = systolic blood pressure below 140 mmHg and diastolic below 90 mmHg; uncontrolled hypertension blood pressure values above the normal.

*n = 205; **n = 209; ***n = 212.

Table 2. Diabetic retinopathy prevalence in the study population according to the International Clinical Classification of Diabetic Retinopathy and Macular Edema

	Gold standard*	FP 1	FP 2	FP 3
Diabetic retinopathy *n* (%)				
No apparent DR	164 (74.9%)	155 (70.8%)	154 (70.3%)	170 (77.6%)
Mild NPDR	7 (3.2%)	21 (9.6%)	21 (9.6%)	20 (9.1%)
Moderate NPDR	24 (11%)	10 (4.6%)	8 (3.7%)	14 (6.4%)
Severe NPDR	5 (2.3%)	9 (4.1%)	10 (4.6%)	3 (1.4%)
Proliferative DR	3 (1.4%)	10 (4.6%)	13 (5.9%)	1 (0.5%)
Impossible to classify	16 (7.3%)	14 (6.4%)	13 (5.9%)	11 (5%)
Diabetic macular edema, *n* (%)				
No apparent ME	186 (84.9%)	195 (89%)	192 (87.7%)	204 (93.2%)
Mild	4 (1.8%)	7 (3.2%)	5 (2.3%)	4 (1.8%)
Moderate	4 (1.8%)	1 (0.5%)	7 (3.2%)	—
Severe	2 (0.9%)	2 (0.9%)	2 (0.9%)	—
Impossible to classify	23 (10.5%)	14 (6.4%)	13 (5.9%)	11 (5%)

FP, family physicians; NPDR, nonproliferative diabetic retinopathy.

*Ophthalmologists.

(average, 92%), as was accuracy, ranging from 88.2% to 93% (average, 90.3%). The positive predictive value, i.e., the proportion of subjects correctly diagnosed with DR, ranged from 68% to 75.5% (average, 71.2%); this resembles values previously reported in the literature of 62% (12) and 76% (13).

Regarding DME evaluation, sensitivity and positive predictive values were poor (sensitivity for assessment by FPs ranged from 10% to 70% and positive predictive value from 10% to 50%), but specificity and accuracy were very good, with a mean specificity of 96.6% (95.1–98.4%) and accuracy of 93.1% (90.7–94.9%). This was expected because the sample was not calculated for evaluation of DME. For the sample to be powered to calculate agreement between observers, estimating a kappa score above 0.8 and a 6.8% prevalence of DME, would have required 473 participants. Moreover, two-field digital retinal photography has limited value for assessment of DME, which should be further evaluated with a combination of techniques (biomicroscopy, optical coherence tomography, and stereoscopic analysis of the retina) (10). There may have been some problem with the training, but method is not suitable for visualization of macular edema. There was even no complete agreement among ophthalmologists.

Table 3. Performance of family physicians (FP) and ophthalmologists (gold standard) for screening of diabetic retinopathy (DR) and Diabetic macular edema (DME)

	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Positive agreement (%)	Negative agreement (%)
DR FP 1	94.8	92.6	93	75.5	76.0	99.5
DR FP 2	87.2	90.2	89.6	68	66.0	94.0
DR FP 3	66.7	93.3	88.2	70.2	60.0	94.0
DME FP 1	10	95.1	90.7	10	10.0	95.0
DME FP 2	70	96.2	94.9	50	58.0	97.0
DME FP 3	10	98.4	93.8	25	58.0	93.0

Table 4. Evaluation of agreement in diabetic retinopathy (DR) and diabetic macular edema (DME) classification between family physicians (FP) and ophthalmologists (gold standard)

	Percent agreement	Concordance measures	
	%	Kappa	Adjusted kappa
DR FP 1	83.7	0.57 (0.47 to 0.67)	0.80
DR FP 2	79.8	0.47 (0.37 to 0.57)	0.75
DR FP 3	79.3	0.37 (0.26 to 0.48)	0.74
DME FP 1	90.8	0.067 (–0.12 to 0.25)	0.88
DME FP 2	93.9	0.48 (0.28 to 0.67)	0.92
DME FP 3	93.8	0.12 (–0.12 to 0.37)	0.92

Table 5. Effect of pupillary dilation on the readability of retinal photographs in the sample overall and stratified by age

Readability	Without dilation*	With dilation*
Overall (n = 183)[a]		
Unreadable	27 (14.8%)	16 (8.7%)
Questionable	42 (23.0%)	31 (16.9%)
Legible	114 (62.3%)	136 (74.3%)
Age less than 65 years (n = 89)[b]		
Unreadable	4 (4.5%)	3 (3.4%)
Questionable	20 (22.5%)	14 (15.7%)
Legible	65 (73.0%)	72 (80.9%)
Age 65 or older (n = 94)[c]		
Unreadable	23 (24.5%)	13 (13.8%)
Questionable	22 (23.4%)	17 (18.1%)
Legible	49 (52.1%)	64 (68.1%)

*N (%).
[a]McNemar test, P = 0.008.
[b]McNemar test, P = 0.579.
[c]McNemar test, P = 0.011.

Kappa statistics range from 0 to 1, with 0 representing random agreement and 1 denoting perfect agreement. The cutoffs for categorization of kappa coefficients in this study were: 0.61–0.80, good agreement; 0.81–1.0, very good agreement. However, it should be taken into account that the kappa statistic is highly dependent on prevalence. To overcome this limitation, we adjusted kappa coefficients for prevalence in our sample. The coefficients thus adjusted showed good agreement between FPs and the gold standard for DR detection, and very good agreement for DME. Percent agreement of FP, compared with the gold standard, ranged from 79.3% to 83.7% for DR and 90.8% to 93.9% for DME. This is in line with the existing literature, in which values of 89–97.5% (14) and 91–93% (15), respectively.

Unlike other countries, Brazil has no structured, systematic system for DR screening. Therefore, policy planners in the country should consider how access is achieved, how the quality of screening can be assured, and, ultimately, how to provide conditions for treatment of diagnosed cases. The present study demonstrates that trained FPs can contribute to such a screening program.

Screening strategies that use digital images of the retina are an alternative to facilitate treatment access in the public health system. Multidisciplinary teams including FPs, endocrinologists, ophthalmologists, and optometrists have participated in the systematic screening systems deployed in other countries and helped develop such systems while considering particular conditions and local culture (5). In the UK, screening is carried out with digital photography and covers 80–99% of diabetics over age 12 years. In England, two-field fundus photography is performed with fixed or mobile cameras, and images are evaluated remotely at reading centres. In Wales, screening is performed by a screening team that uses 30 cameras at 220 sites, with photos obtained after mydriasis and analysed immediately (16). In Ireland, FPs recruit diabetics and retinal images are captured and analysed by optometrists; patients with significant retinal lesions are referred to an ophthalmologist (17). In Scotland, a single photograph is obtained after mydriasis and analysed via software. In France, several forms of screening are used, including analysis of fundus photographs by software, by orthoptists (non-medical technicians), and by nurses, with ophthalmologist referral of patients with abnormalities. Spain has reported a screening experiment performed by FPs working with ophthalmologists (5). In the USA, there have been several screening experiments using imaging centres and telemedicine (18).

In our sample, pupil dilation was associated with better examination quality only in elderly patients. However, not included in the analysis are other factors associated with the need for dilation, such as pupil size and presence of diabetic neuropathy, which is a limitation of this study.

The usual gold standard for DR diagnosis is seven-standard-field stereoscopic colour fundus photography supplemented by a comprehensive dilated eye examination with slit-lamp examination of the retina (3). In this study, the gold standard was established from an evaluation of the photographs by two experienced ophthalmologists. Although this is a weakness of the study, it approaches the reality of Brazil, where the initial evaluation of patients is done exclusively by ophthalmologic examination.

According to the gold standard, 68.5% of patients would not need to be referred for further evaluation by an ophthalmologist. The FPs did not refer 60.6% of participants, including patients referred due to poor photo readability, RD, DME and other reasons. In Spain, in a similar study, FPs referred 57.2% of screened patients for further evaluation by an ophthalmologist (19).

Although the study sample was not random, the prevalence of DR in this study was similar to that found in other investigations

conducted in primary care (1, 2), which helps corroborate our results. As expected, the patients with most severe retinopathy also had higher blood pressure and worse glycemic control (1, 2).

Our sample consisted mostly of white participants (89%), which is consistent with the ethnic distribution of the population in our coverage area, which is 92.99% white (20); however, it reduces the applicability of our findings to other ethnic groups.

Conclusions

We believe a high-quality primary-care diabetic retinopathy screening program can be organized in Brazil, with initial screening performed by FPs. Pharmacologic mydriasis can be restricted to cases in which a high-quality fundus photograph cannot be obtained without dilation, mainly in elderly patients. Image analysis can be performed by ophthalmologists via telemedicine or by trained FPs. Further studies should be designed to assess the time range for screening mild forms of retinopathy, to assess the logistics of screening in health districts and at the municipal level, and to evaluate the cost-effectiveness of the process.

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Conflict of interest: none.

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