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Optical coherence tomography and contrast sensitivity in early diabetic retinopathy

Hadi Ostadimoghadam[1], Toktam Helmi[2], Abbasali Yekta[3], Javad Heravian Shandiz[1], Hojat Shafaei[1], Hamed Momeni Moghadam[4], Monireh Mahjoob[4]*

Abstract:

PURPOSE: This study used contrast sensitivity (CS) and optical coherence tomography (OCT) to assess the functional and structural alterations of the macula and the optic nerve head (ONH) in diabetic patients with no retinopathy and those with mild nonproliferative diabetic retinopathy (NPDR).

MATERIALS AND METHODS: In this study, 40 eyes of 20 diabetic patients with no diabetic retinopathy (DR), 40 eyes of 20 diabetic patients with mild NPDR, and 36 eyes of 18 healthy individuals were examined. Best-corrected visual acuity (VA) and CS were performed using early treatment DR study charts and the Pelli-Robson chart, respectively. The macula and ONH were evaluated using OCT, which provided data on the entire retina, inner retinal layer, outer retinal layer, retinal nerve fiber layer (RNFL), and the macula zone-ellipsoid zone-retinal pigment epithelium layer.

RESULTS: VA and CS were significantly different between the three groups ($P < 0.001$). The entire thickness of the retina and the internal thickness of the retina in the 3–6 mm subfields of the macular region, as well as the thickness of the ganglion cell layer + inner plexiform layer (GCL + IPL) and GCL + IPL + RNFLs, differed significantly across the groups ($P < 0.013$).

CONCLUSION: In diabetic subjects with no retinopathy, the reduced thickness of the GCL + IPLs is possibly indicative of early neurodegenerative changes in the inner retina. Furthermore, in the diabetic groups, a decrease in CS was observed compared to the control group.

Keywords:

Contrast sensitivity, diabetic retinopathy, retinal nerve fiber layer, retinal thickness, visual acuity

[1]Refractive Errors Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [2]Department of Eye Diseases, Farabi Hospital, Mashhad, Iran, [3]Department of Optometry, School of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, Iran, [4]Department of Optometry, Rehabilitation Sciences Research Center, Faculty of Rehabilitation, Zahedan University of Medical Sciences, Zahedan, Iran

***Address for correspondence:**
Dr. Monireh Mahjoob, Department of Optometry, Rehabilitation Sciences Research Center, Faculty of Rehabilitation, Zahedan University of Medical Sciences, Zahedan, Iran.
E-mail: mahjoob_opt@yahoo.com

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Introduction

Diabetes mellitus, a group of metabolic diseases, is a rising global epidemic characterized by hyperglycemia, which is in turn caused by defects in insulin secretion, insulin action, or both. Diabetes-related chronic hyperglycemia is associated with long-term organ damage and dysfunction, particularly in the eyes.[1] As one of the main causes of preventable blindness, diabetic retinopathy (DR) has been considered a retinal microcirculatory disease.[2] Numerous factors may contribute to DR-related vision loss, including preretinal or vitreous hemorrhage, retinal detachment, neovascular glaucoma, macular edema or capillary nonperfusion, and associated neovascular glaucoma.[3] Roughly 75% of patients with diabetes mellitus are affected by DR 15 years after diagnosis. It has been confirmed that the prevalence and severity of retinopathy vary in different ethnicities.[4,5] DR has a 41.9% prevalence rate in Iranian diabetic patients,[6] outnumbering the cases in other countries.[3,7,8] The identification of visible vascular changes, such as hemorrhages, neovascularization, and blood vessel leakage, is the foundation of the current guidelines for diagnosing, staging, and managing DR.[9] However, there is

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mounting evidence that retinal neurodegeneration plays a role in developing microvascular abnormalities as an early event in DR pathogenesis.[2] As a result, dysfunction of the neuroretina may occur before the typical vascular findings.[2]

One of the standard tests for visual function is visual acuity (VA). However, numerous studies have demonstrated that contrast sensitivity (CS) is a more sensitive indicator of retinal neuropathy.[10,11] Before the clinical onset of retinopathy, diabetic subjects exhibit decreased CS.[10,12] It has been discovered that CS declines significantly in patients with no clinical evidence of DR and those with mild DR, making it the most sensitive test for early-stage DR.[10] Therefore, the detectability of subtle differences in DR using CS may be useful for early monitoring of retinal function in diabetes and predicting and screening DR.[10,12]

Retinal neuropathy in DR is characterized by structural changes, including neuronal apoptosis in retinal layers[13] and retinal nerve fiber layer (RNFL) thinning in diabetes.[10,14,15] As evidence of early neurodegeneration, the RNFL of diabetic patients with no DR is thinner than that of healthy controls.[15] Previous research has demonstrated that changes visible on optical coherence tomography (OCT) imaging are associated with visual impairment in diabetic patients with early-stage DR.[10] Thus, the combination of OCT-defined retinal structure and quantitative assessment of visual function can detect retinal neurodegeneration and prevent DR-related vision loss through early detection and prompt treatment.

Although all ethnic groups are susceptible to DR, ethnic-specific risk factors may affect the rate and severity of DR,[4,5] so the primary objective of this study was to compare CS and the changes in the thickness of selected retinal layers both in the macula and the peripapillary area using spectral-domain-OCT, in Iranian diabetic patients with no DR and with mild nonproliferative DR (NPDR) to normal subjects.

Materials and Methods

In this study, 40 eyes of 20 diabetic patients with no diabeticretinopathy (DR), 40 eyes of 20 diabetic patients with mild NPDR, and 36 eyes of 18 healthy individuals were examined. This cross-sectional study, which was conducted in a private ophthalmology office specializing in the posterior segment of the eye, was conducted as per the Declaration of Helsinki and was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1399.475). All participants in the study provided a signed, written consent form.

Eye examinations, including slit lamp biomicroscopy and fundoscopy, were performed on all subjects with dilated pupils using a 90+ lens and also, intraocular pressure was measured by an Air Puff (noncontact) Keeler Tonometer (Pulsair intelliPuff Keeler tonometer). Individuals with diabetes were split into two groups based on early treatment DR study (ETDRS)-approved criteria: those with no DR and those with mild NPDR. The inclusion criteria for the diabetic patients were a minimum age of 40 and a diagnosis of Type II diabetes mellitus. The control group comprised healthy individuals without diabetes. The inclusion criteria for the control group included a minimum age of 40, the absence of a clinical diagnosis of diabetes, and a hemoglobin $A1_C$ ($HbA1_C$) level below 5.7%. $HbA1_C$ was measured 1 week before the examination for all participants in a private hematology laboratory.

Exclusion criteria for all three groups included the presence of a systemic disease other than diabetes, the presence of eye diseases such as macula diseases, cataracts, glaucoma, or keratoconus, a history of eye surgery or laser treatments on the eye, refractive errors >± 3, the presence of proliferative DR and macular edema, and poor quality retinal imaging with OCT.

After correcting refractive errors, the best-corrected VA was measured using ETDRS charts, and CS was assessed using the Pelli-Robson chart at a distance of 1 m. Monocular VA and CS were assessed under standard photopic lighting conditions.

OCT (REVO NX) (Optopol Technology Ltd, Zawiercie, Poland) was utilized to measure the thickness on the macula and optic nerve head (ONH) (software version 9.5). This device employs a wavelength of 830 nm. Four quadrants of the macula and ONH were scanned. The thicknesses of the macula were measured in the nine subfields of the ETDRS regions. The device provided information regarding the entire retina thickness, the inner retinal layer thickness (the distance between the internal limiting membrane and the external limiting membrane), the outer retinal layer thickness (the distance between the external limiting membrane and the outer border of the retinal pigment epithelium [RPE] layer), the RNFL, ganglion cell layer + inner plexiform layer (GCL + IPL), and the macula zone-ellipsoid zone-RPE layer (MZ-EZ-RPE).

version 15 of the SPSS Statistical Package (Chicago, IL, USA, SPSS Inc) was used for data analysis. The repeated measures ANOVA test was utilized to compare the measured thicknesses of the three groups. Pairwise comparisons with Bonferroni correction were reported as mean and 95% confidence intervals (CIs) of differences. The significance level was set at $P < 0.05$.

Results

This study examined 40 eyes of 20 diabetic people with no DR, 40 eyes of 20 diabetic people with mild NPDR, and 36 eyes of 18 healthy people. Table 1 displays the demographic characteristics of the three groups. According to the ANOVA statistical test, there was no significant difference in average age among the three groups ($P = 0.19$). In contrast, the groups had significantly different in HbA1c levels ($P < 0.001$).

VA and CS were significantly different between the three groups ($P < 0.001$). A pairwise comparison with Bonferroni correction revealed a significant difference in VA and CS between healthy subjects and mild DR (VA: 0.027, 95% CI: 0.011, 0.043; $P < 0.001$, CS: 6.1, 95% CI: 1.3, 10.9; $P = 0.007$) and between the mild NPDR and no DR (VA: 0.023, 95% CI: 0.007, 0.039; $P = 0.002$, CS: 7.1, 95% CI: 2.4, 11.8; $P = 0.001$). There was a significant correlation between VA and CS ($P = 0.035$, $r = -0.217$).

Figure 1 depicts the thickness of the entire retina, as well as the thickness of the inner and outer retinal layers, for the three groups. Based on repeated measures of ANOVA, no significant differences were found in the thickness of the outer retinal layer between the three groups ($P = 0.556$). The thickness of the entire retina ($P = 0.011$) and the inner thickness of the retina ($P = 0.005$) were significantly different between the three groups in the 3–6 mm subfields of ETDRS grid regions. A pairwise comparison confirmed this difference between the diabetic groups with no DR and with mild NPDR (entire retinal thickness: 0.32, 95% CI: 1.66, 14.97; $P = 0.009$, inner retinal thickness: 7.39, 95% CI: 2.06, 12.72; $P = 0.003$).

Table 2 displays the GCL + IPL layers thickness for the three groups. The GCL + IPL thickness varied significantly among the three groups ($P = 0.005$) (No DR vs. control: 3.15, 95% CI: 0.016, 6.29; $P = 0.048$, mild NPDR vs. No DR: 4.33, 95% CI: 0.96, 7.69; $P = 0.007$).

In addition, there was a statistically significant difference in RNFL + GCL + IPL thickness between groups ($P = 0.013$) (mild NPDR vs. No DR: 5.35, 95% CI: 1.01, 9.69; $P = 0.010$).

Tables 3 and 4 present the thickness of RNFL, the MZ-EZ-RPE layers, and the thickness of nerve fiber layers (NFLs) in the ONH in each group, respectively. Repeated measures ANOVA revealed that the thickness of the RNFL ($P = 0.163$), the thickness of the MZ-EZ-RPE ($P = 0.585$), and the thickness of the NFL in the investigated quadrants of ONH ($P = 0.195$) did not differ significantly between groups.

Pearson's correlation showed that there was no significant relationship between CS and the thickness of the investigated layers in the two diabetic groups ($P > 0.171$).

Table 1: Demographic characteristics of the participants in three groups (mean±standard deviation)

Groups	Control	No DR	Mild NPRDR	*P*
Number (patient/eye)	18/36	20/40	20/40	
Age (years)	55.2±4.2	58.4±4.5	57.2±5.8	0.19
HgA1C (%)	5.2±0.2	7.1±1.1	8.1±1.3	<0.001*
VA (logMAR)	−0.02±0.25	−0.01±0.28	0.005±0.02	<0.001*
CS (log contrast)	162.5±7.4	161.4±8.3	155.3±7.3	0.001*

*=Significant difference, DR=Diabetic retinopathy, NPRDR=Nonproliferative diabetic retinopathy, VA=Visual acuity, logMAR=Logarithm of the minimum angle of resolution, CS=Contrast sensitivity

Discussion

Currently, diabetes is one of the world's leading causes of blindness.[16] Given the importance of early detection of retinal disorders in diabetes, this study used OCT to

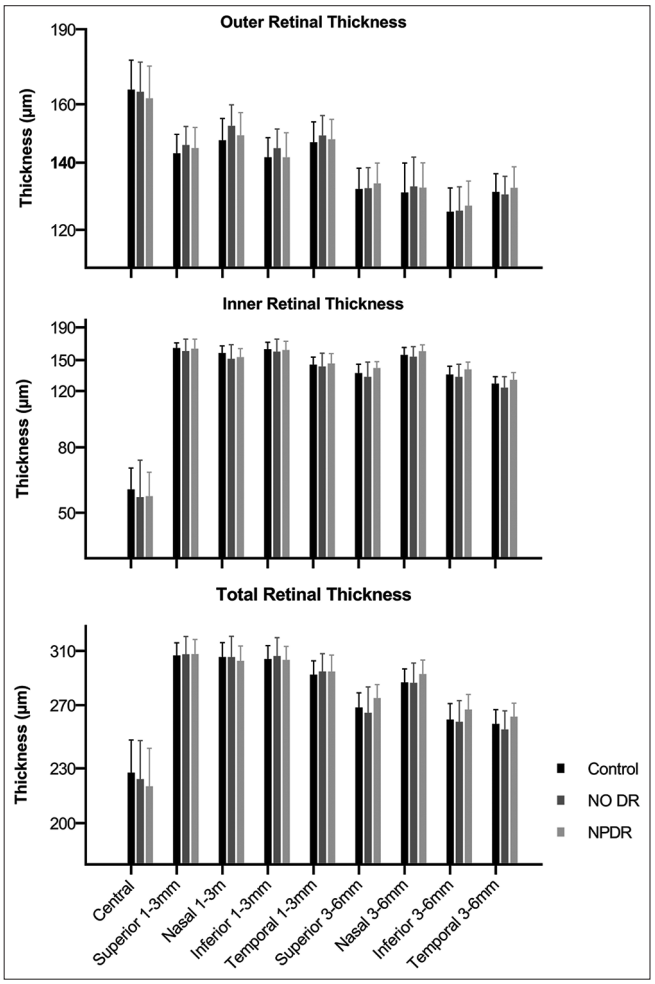

Figure 1: The mean ± standard deviation of the entire retinal thickness and inner and outer retinal thickness in study groups DR = Diabetic retinopathy, NPDR = Nonproliferative diabetic retinopathy

Table 2: The mean±standard error of mean of the ganglion cell layer + inner plexiform layer and retinal nerve fiber layer + ganglion cell layer + inner plexiform layer in study groups

Groups	Control	No DR	Mild NPRDR	*P*
GCL + IPL				
Superior	87.91±0.81	85.5±1.2	89.3±1.0	0.05
Superior nasal	89.91±0.83	86.4±1.1	90.3±0.8	0.009*
Inferior nasal	89.22±0.82	85.8±1.06	89.8±0.9	0.008*
Inferior	87.80±0.88	84.3±1.07	89.1±1.0	0.003*
Inferior temporal	86.21±0.80	82.82±1.3	87.8±1.1	0.006*
Superior temporal	84.0±0.75	81.2±1.2	85.7±0.9	0.01*
NFL + GCL + IPL				
Superior	119.1±0.8	116.9±1.6	122.2±1.2	0.028*
Superior nasal	121.8±0.9	119.1±1.8	124.3±1.1	0.044*
Inferior nasal	122.3±0.9	119.5±1.6	124.7±1.3	0.039*
Inferior	119.1±0.9	117.0±1.6	122.8±1.3	0.017*
Inferior temporal	109.1±1.1	105.9±1.4	111.3±1.2	0.018*
Superior temporal	106.1±0.9	103.0±1.2	108.0±1.1	0.008*

*=Significant difference, GCL + IPL=Ganglion cell layer+inner plexiform layer, NFL+ GCL +IPL=Nerve fiber layers+ganglion cell layer+inner plexiform layer, DR=Diabetic retinopathy, NPRDR=Nonproliferative diabetic retinopathy

Table 3: The mean±standard error of the mean of retinal nerve fiber layer and macula zone-ellipsoid zone-retinal pigment epithelium layer thickness in study groups

Groups	Control	No DR	Mild NPRDR	*P*
RNFL (mm)				
Central: 1	12.3±0.6	11.1±0.7	10.5±0.5	0.164
Superior: 1-3	26.6±0.4	26.8±0.7	26.8±0.5	0.493
Nasal: 1-3	22.8±0.3	22.3±0.4	22.9±0.4	0.557
Inferior: 1-3	26.6±0.4	26.8±0.7	27.5±0.6	0.601
Temporal: 1-3	20.2±0.3	19.9±0.3	20.7±0.3	0.189
Superior: 3-6	38.3±0.8	37.9±0.9	40.5±0.5	0.097
Nasal: 3-6	47.1±0.7	47.1±1.3	49.5±0.9	0.250
Inferior: 3-6	39.2±0.7	40.0±1.2	42.9±0.8	0.040*
Temporal: 3-6	21.2±0.2	21.1±0.3	22.8±0.7	0.014*
MZ-EZ RPE (mm)				
Central: 1	65.7±0.4	64.7±0.3	64.2±1.6	0.459
Superior: 1-3	63.1±0.3	63.0±0.2	63.7±0.4	0.279
Nasal: 1-3	63.5±0.3	63.2±0.2	63.8±0.4	0.375
Inferior: 1-3	64.1±0.5	63.6±0.3	64.6±0.6	0.413
Temporal: 1-3	63.5±0.3	63.3±0.2	63.8±0.4	0.539
Superior: 3-6	65.6±0.5	65.3±0.5	65.2±0.7	0.820
Nasal: 3-6	68.7±0.8	67.6±0.6	68.3±1.1	0.611
Inferior: 3-6	69.4±0.8	67.7±0.6	68.4±1.0	0.328
Temporal: 3-6	67.1±0.7	66.6±0.6	65.9±0.8	0.556

*=Significant difference, RNFL=Retinal nerve fiber layer, MZ-EZ RPE=Macula zone-ellipsoid zone-retinal pigment epithelium layer, DR=Diabetic retinopathy, NPRDR=Nonproliferative diabetic retinopathy

compare the thickness of the macula and ONH between healthy subjects and diabetic patients with no DR and those with mild NPDR. In addition, CS was assessed as one of the visual functions contributing to the early diagnosis of retinal disorders in these individuals. In comparison to the healthy group, the diabetic group with no DR and with mild NPDR exhibited variations in the thickness of the inner layers of the retina in the macula.

In this study, diabetic subjects with no DR exhibited decreased GCL + IPL thickness in the macula's superior, inferior, and semi-inferior quadrants. Lim *et al*. also demonstrated decreased GCL + IPL thickness in diabetic subjects with and with no retinopathy, and the rate of reduction was significantly greater in diabetic subjects than in healthy subjects over a 3-year follow-up period.[17] Progressive neurodegeneration in ganglion cells and their axons due to the toxic effects of hyperglycemia in diabetes, which occurs in the early stages of DR[18] One and before clinical DR, is a potential cause of decreased macular GCL + IPL thickness.

The present study revealed an increase in the thickness of the entire retina and inner retinal layer in the 3–6 mm macular region of diabetic subjects with mild NPDR. Furthermore, RNFL + GCL + IPL exhibited increased thickness in mild NPRD patients compared to diabetic individuals with no DR and healthy individuals. Previous studies have yielded inconsistent results. In the study by Oshitari *et al*., the macular thickness in the central sector decreased in diabetic patients with no DR and increased in diabetic patients with proliferative DR, which was incongruent with their findings concerning RNFL thickness changes.[14] Compared to the control group, the decrease in RNFL thickness in the macula in individuals with no DR was not statistically significant.[14] However, there was a significant decrease in macular RNFL thickness in proliferative retinopathy.[14] They stated that the resolution limitation of the stratus OCT device was responsible for this disparity between macular and RNFL thickness changes in diabetic groups.[14] Several studies have not found differences in retinal thickness and RNFL between healthy individuals and diabetic patients with no DR or with mild NPDR,[15,19,20] and attributed this to good metabolic control of the patients.[15] On the contrary, Goebel and Kretzchmar-Gross demonstrated that the increased thickness of the retina in diabetic patients relative to healthy individuals was directly related to the leakage of retinal blood vessels.[21] One of the possible reasons for the increase in the thickness of the retina and RNFL + GCL + IPL layers in mild NPDR obtained in this study could be that neurological abnormalities may precede vascular abnormalities. Therefore, as DR progresses, vascular permeability and other vascular disorders are increased and leads to an increase in retinal thickness in diabetic patients with mild NPDR compared to diabetic patients with no DR.

Table 4: The mean±standard error of the mean of the nerve fiber layer in the optic nerve head in study groups

Groups	Control	No DR	Mild NPRDR	*P*
Superior	138.8±1.7	134.8±2.3	141.7±2.3	0.096
Nasal	105.4±3.1	100.2±2.8	103.8±2.5	0.404
Inferior	142.6±2.1	139.4±2.2	142.3±2.5	0.527
Temporal	73.6±1.4	74.3±1.5	76.5±1.5	0.426

DR=Diabetic retinopathy, NPRDR=Nonproliferative diabetic retinopathy

In this study, there was no significant difference in the thickness of the outer retinal layer between the three groups. Vujosevic's and Midena study also did not show a significant difference in outer retinal thickness between diabetic subjects with no DR and with mild NPDR compared to the control group.[15] In the early stages of diabetes, a study found that changes in astrocytes as a moderator of neuronal and vascular function were accompanied by hypoxia of the inner retinal layers and changes in ganglion cells. In contrast, gliosis of Müller cells and further changes in the outer layers of the retina occurred in the later stages of diabetes.[22] Therefore, one possible reason for these observations is that, at least in the early stages of DR, the outer layer of the retina is not affected by diabetes.

No change in NFL thickness was observed in the ONH based on our findings. Cao's *et al*., study on diabetic subjects with no DR and healthy individuals revealed that microvascular alterations of the ONH occurred before neurodegenerative changes such that a decrease in peripapillary vascular density was observed in all eight quadrants investigated.[23] On the other hand, the decrease in NFL thickness was observed only in the superior nasal, inferior nasal, and superior nasal quadrants.[23] In another study, diabetic subjects with no DR revealed a reduction in peripapillary ONH density in only two of the six quadrants examined; however, there was no difference in peripapillary RNFL thickness between diabetic subjects with no DR and the control group.[24] However, destruction of superficial and deep capillary networks and choroid capillaries in the macula region[25] and microvascular alterations in the ONH have been noted in diabetic patients with no DR.[23] Due to the absence of an OCT angiography, our research cannot explain why there was no change in the NFL thickness of the ONH in diabetic patients.

In this study, compared to the healthy group, diabetic subjects had deteriorated VA and CS. Our results indicated a worsening of VA and CS in the NPDR group compared to the diabetic subjects with no DR, which seems reasonable due to the significant correlation between VA and CS obtained in this study. Considering that this decrease in VA and CS was observed in the diabetic groups compared to the normal group of the same age, the reason for this decrease may be due to the problems caused by diabetes. Visual functional changes have been observed in diabetic subjects before severe vascular defects are clinically detectable.[26] It was found that diabetic patients with no DR exhibited a reversible decrease in CS with good metabolic control in high spatial frequency.[27] On the contrary, subjects with preproliferative DR and proliferative DR exhibited an irreversible decrease in CS in all spatial frequencies with good metabolic control.[27] Due to the lack of significant correlation between the CS and the thickness of the investigated layers in the two diabetic groups in the present study, the reason for the decrease in CS cannot be generalized with certainty to the potential effects of retinal neurodegeneration or vascular abnormalities. More studies are needed to investigate the direct relationship between visual functions and retinal structural changes in diabetic patients.

One of the limitations of the current study is the absence of OCT angiography, which would have allowed for a more precise examination of the causes of changes in NFL in ONH and macular thickness in diabetic groups with no DR and with mild NPDR compared to healthy individuals.

Conclusion

Reduced thickness of the GCL + IPL layers in diabetic subjects with no DR in this study is possibly indicative of early neurodegenerative changes in the inner retina since the thickness difference is not huge and later disappeared in the mild NPDR group. On the other hand, increased thickness of the GCL + IPL and GCL + IPL + RNFL layers in diabetic patients with mild NPDR can indicate vascular disorders and increased permeability of blood vessels as DR progresses.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interest of this article.

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