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Original article

Decrease in inner retinal thickness at para- and perifoveal areas before vascular retinopathy in patients with metabolic risk factors

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ABSTRACT

Background: Hypertension, dyslipidemia, and hyperglycemia are major risk factors for vascular retinopathy. The relationship between retinal thickness at the macular area and metabolic risk factors, as well as visual impairment, in elderly patients before developing vascular occlusion needs to be investigated.

Methods: In this prospective, case-control study, patients >60 years old, without objective visual threatened ocular diseases or systemic abnormalities, except for hypertension, dyslipidemia or/and hyperglycemia, were included for measurement of retinal thickness at the macular area by optical coherence tomography (OCT).

Results: Fifty-four patients were analyzed; 11 patients had no metabolic risk factors, 16 had one, 17 had two, and 10 had three. There was no significant difference in age, and full and outer retinal thickness, but there was a significantly lower inner retinal thickness at the parafoveal ($p = 0.0013$) and perifoveal ($p = 0.018$) areas in patients with at least one metabolic risk factor. The superior ($p = 0.040$) and inferior ($p = 0.046$) inner retina at the perifovea and superior ($p = 0.013$) inner retinal thickness at the parafovea were sensitive to metabolic abnormalities. Only patients with three factors had significantly reduced best corrected visual acuity (BCVA).

Conclusion: Elderly patients with metabolic risk factors had decreased inner retinal thickness at the para- and perifoveal areas before retinal vascular diseases. Accelerated inner retinal degeneration occurred prior to visual impairment.

1. Introduction

Metabolic syndrome is a constellation of abnormalities in metabolic homeostasis, including glucose intolerance, insulin resistance, dyslipidemia, central obesity, and hypertension.[1–3] The worldwide increased prevalence of metabolic syndrome contributing to the mortality of cardiovascular diseases, has been a major public health problem.[4–7] It is known that retinal vascular diseases, such as retinal artery occlusion, retinal vein occlusion, diabetic retinopathy with vascular leakage, hemorrhage or neovascularization, attack visual acuity complicated with irreversible visual disturbance. Hypertension, dyslipidemia, and hyperglycemia, are the most common risk factors for retinal vascular diseases.[8–10] Moreover, more metabolic risks are associated with the higher incidence of diabetic complications,[11] and diabetic patients with concomitant metabolic syndrome suffer from a higher prevalence of macro- and microvascular diseases, including retinopathy.[11,12] The above findings implicated the possible role of metabolic risks in visual outcome.

Diabetes- or retinal vascular occlusion-related macular edema leads to severe visual disturbance,[13,14] and optical coherence tomography (OCT) provides a noninvasive approach to accurately measure retinal thickness at macular areas.[15,16] Increase in macular thickness due to macular edema diagnosed by OCT has been widely used in clinical ophthalmology.[17,18] However, only a handful of investigations of the macular thickness in diabetic or vascular retinopathy without macular edema have been reported.[19–22] In

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animal experiments, neuroglial tissue loss could be observed before any sign of vasculopathy at the early stage of diabetic retinopathy.[19–21] It has been reported that a significant decrease in pericentral retinal thickness could be detected by OCT in patients of type 1 diabetes mellitus with early diabetic retinopathy,[22] indicating that progressive loss of thickness at the macular area occurred before advanced retinopathy induced by hyperglycemia.

In fact, the relationship among retinal thickness, visual acuity and metabolic risk factors has not been clearly established. The purpose of this study is to investigate the effect of hypertension, dyslipidemia and hyperglycemia on macular thickness in elderly patients without retinal vascular diseases. In this study, patients were divided into four groups according to their cumulative metabolic risks. Full, inner and outer retinal thickness at the central foveal, parafoveal and perifoveal areas, respectively, were measured by OCT. Best corrected visual acuity (BCVA) in each group was also analyzed.

2. Methods

2.1. Inclusion and exclusion criteria

An Institutional Review Board approval from Wan Fang Hospital, Taipei Medical University was obtained prior to the commencement of this study. Patients >60 years old, with or without metabolic risk factors (hypertension, dyslipidemia, or hyperglycemia), from the outpatient clinic of the department of ophthalmology at Wan Fang Hospital, were included for the measurement of macular thickness by OCT and complete ophthalmic evaluation, including BCVA measurement by an auto Ref/Keratometer (Nidek ARK-710A; Nidek Co. Ltd, Gamagori-shi, Aichi, Japan), pneumotonometer measurement of intraocular pressure (Nidek NT-2000, Nidek Co. Ltd), corneal, anterior segment and lens evaluation under slit lamp microscopy (Nidek SL-1600, Nidek Co. Ltd), and vitreous and eye ground examination under pupil dilation by indirect microscopy (Welch Allyn 12500; Welch Allyn Inc., Skaneateles Falls, NY, USA). The metabolic risk factors were confirmed by three independent blood pressure measurements (Omron HEM-1000, Omron, Taipei, Taiwan), blood tests, including fasting blood sugar (Beckman Coulter, Inc., Brea, CA, USA), glycated hemoglobin (Tosoh, Tokyo, Japan), triglyceride, total cholesterol, low-density lipoprotein and high-density lipoprotein (Beckman Coulter) within 6 months. Among these patients, anyone who suffered from a visual threatened ocular disease, such as opaque cornea and vitreous, glaucoma, cataract (nuclear color > grade 2 according to the lens opacities classification system III[23] or any grade of cortical cataract and posterior subcapsular cataract), uveitis, or any kind of choroidopathy, retinopathy (including diabetic retinopathy, age-related macular degeneration, myopic retinopathy), retinal vascular occlusion, retinal hemorrhage, vascular leakage, neovascularization, optic neuropathy, as well as abnormality detectable on OCT, such as macular/retinal edema, cystic lesion, neovascular lesions, and macular hole, were excluded. Furthermore, patients with a history of any kind of acute visual loss, or with a systemic abnormality

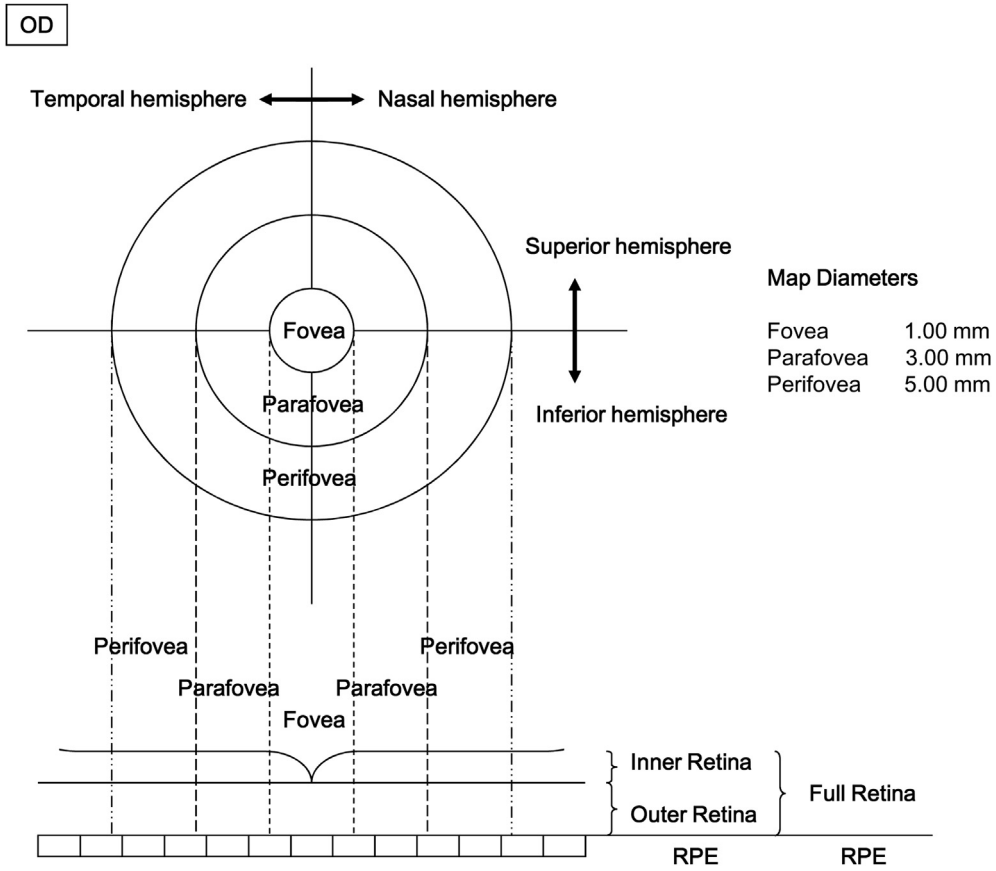

Fig. 1. Illustration of retinal thickness measurement. The full sensory retina was divided into the outer retina and inner retina. Retinal thickness at the macular area was divided into the fovea (0–1 mm diameter from central fovea), parafovea (1–3 mm diameter from central fovea), and perifovea (3–5 mm diameter from central fovea). The superior and inferior hemispheres were divided by the horizontal line crossing the central fovea, while the nasal and temporal hemispheres were divided by the vertical line crossing the central fovea.

Table 1
The definition of metabolic risk factors in our study.

Risk factor (IDF[a] 2005)		
Dyslipidemia	Raised triglycerides	≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
	Reduced HDL[b] cholesterol	<40 mg/dL (1.03 mmol/L) in males <50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Hypertension	Systolic BP[c] ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension	
Hyperglycemia	FPG[d] ≥100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes	

[a] IDF = International Diabetes Federation.
[b] HDL = high-density lipoprotein.
[c] BP = blood pressure.
[d] FPG = fasting plasma glucose.

other than hypertension, dyslipidemia or hyperglycemia, were also excluded. Patients with preexisting renal insufficiency unrelated to metabolic risks were excluded.

2.2. Measurement of retinal thickness by OCT

Retinal thickness at the macular area was measured by RTVue-100 Fourier-domain OCT (Optovue Inc., Fremont, CA, USA). The protocol of the scan in this study was EMM5 with 0.90 seconds duration, which covered a 6 mm × 6 mm area of the macula, with 21 horizontal and 21 vertical scans. This data was used to render a 5 mm × 5 mm map, and could be segmented for presentation of the inner, outer and full retina thickness maps. The full retinal thickness was measured from the vitreoretinal interface (VRI) to the photoreceptor inner segment/outer segment (IS/OS) junction, the outer retinal thickness was from the IS/OS to the inner plexiform layer (IPL), and the inner retinal thickness was from the IPL to the VRI, as per the manufacturer's instructions. The macular area was separated into three concentric circles: the fovea (central circle, with a diameter of 1 mm), the parafovea (inner diameter of 1 mm and outer diameter of 3 mm) and the perifovea (inner diameter of 3 mm and outer diameter of 5 mm) (Fig. 1) according to the protocol of EMM5.

2.3. Definition of metabolic risks

Hypertension, hyperglycemia and dyslipidemia were identified on the basis of the new definition of International Diabetes Federation (IDF) in 2005,[2] which is summarized in Table 1. In this study, patients were divided into four groups according to the number of metabolic risk factors (0, 1, 2 and 3). Patients with no metabolic risk factor (0) served as controls.

2.4. Statistical analyses

Statistical analysis was performed using the Statistical Package for Social Science-10 software (SPSS Inc., Chicago, IL, USA). A comparison of the differences in age, BCVA, and retinal thickness in patients with and without metabolic risks was analyzed by the student t test ($p < 0.05$ or $p < 0.01$). Data of age, BCVA, and retinal thickness among the four groups were analyzed by analysis of variance (ANOVA) with Tukey's post-hoc tests at 95% confidence intervals. In the tables, different alphabet characters represent different levels of significance.

3. Results

Fifty-four patients (24 males, 30 females), aged 60 years to 89 years (mean age = 70.8 years), were included in this study. Among those patients, 11 had no metabolic risk factor (0 risk), 16 had one (1 risk), 17 had two (2 risks), and 10 had three metabolic risk factors (3 risks). Among all patients, 24 suffered from hypertension, 28 had dyslipidemia, and 28 had hyperglycemia (Fig. 2A). The detailed patient profiles are summarized in Table 2 and Fig. 2A.

In patients with hypertension, there were seven patients in the one risk group (hypertension only), seven in the two risk group (combination of hypertension and dyslipidemia or hyperglycemia) and 10 in the three risk group (Fig. 2B). However, only three patients with dyslipidemia belonged to the one risk group, 15 belonged to the two risk group, and 10 belonged to the three risk group (Fig. 2C). There were six hyperglycemic patients in the one risk group, 12 in the two risk group, and 10 in the three risk group (Fig. 2D). In all patients, the retinal thickness was measured by OCT. As shown in Fig. 1, we collected data of full, inner and outer retinal thickness at the macular area. Moreover, the macular area was separated into three circles including the central fovea, the parafovea, and the perifovea.

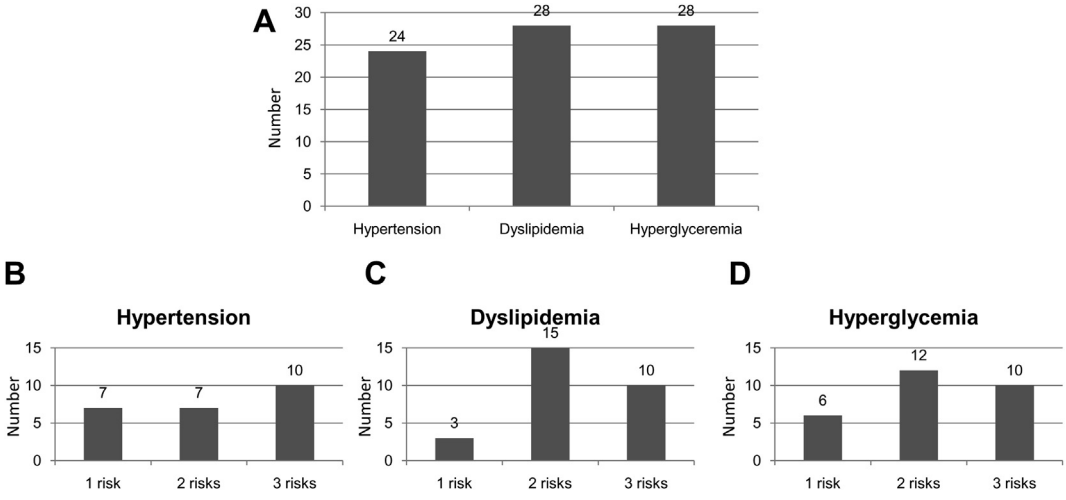

Fig. 2. Analysis of metabolic risks. (A) In this study, 24 patients suffered from hypertension, 28 patients had dyslipidemia and 28 patients had hyperglycemia. Among the patients with hypertension (B), dyslipidemia (C) or hyperglycemia (D), patients were divided by their accumulated metabolic risk factors.

Table 2
Summary of patient data.

No.	Gender	OD/OS	Age (y)	BCVA (log/Mar)	Risk factor		
					Hypertension	Dyslipidemia	Hyperglycemia
Total number = 54							
Male:Female = 24:30							
Mean age (y): 70.8 ± 8.61							
0 risks ($n = 11$)							
1	F	OD	67	0.4	N	N	N
2	F	OS	60	0.7	N	N	N
3	F	OD	84	0.7	N	N	N
4	F	OD	60	0.5	N	N	N
5	F	OS	73	0.7	N	N	N
6	F	OD	60	0.6	N	N	N
7	F	OS	74	0.8	N	N	N
8	F	OD	63	0.4	N	N	N
9	F	OS	70	0.8	N	N	N
10	F	OS	60	0.5	N	N	N
11	M	OD	60	0.9	N	N	N
1 risk ($n = 16$)							
1	M	OS	86	0.3	Y	N	N
2	M	OD	79	0.5	Y	N	N
3	M	OS	79	0.4	N	N	Y
4	M	OD	70	0.6	Y	N	N
5	F	OD	81	0.2	Y	N	N
6	F	OS	81	0.2	N	N	Y
7	M	OD	76	0.4	N	N	Y
8	F	OS	63	0.1	N	Y	N
9	M	OD	63	0.6	N	N	Y
10	F	OD	74	0.5	Y	N	N
11	F	OD	67	0.5	N	Y	N
12	M	OS	63	0.6	N	N	Y
13	F	OS	67	0.3	N	Y	N
14	F	OS	74	0.5	Y	N	N
15	F	OD	66	0.9	N	N	Y
16	F	OS	66	0.9	Y	N	N
2 risks ($n = 17$)							
1	F	OD	68	0.3	N	Y	Y
2	M	OD	67	0.9	N	Y	Y
3	M	OS	70	0.4	Y	Y	N
4	M	OD	65	0.3	N	Y	Y
5	M	OD	77	0.9	N	Y	Y
6	M	OS	85	0.4	N	Y	Y
7	M	OS	61	0.2	Y	N	Y
8	M	OS	81	0.5	Y	N	Y
9	F	OS	76	0.4	Y	Y	N
10	F	OD	64	0.5	Y	Y	N
11	M	OS	64	0.7	N	Y	Y
12	F	OD	74	0.5	N	Y	Y
13	M	OS	67	0.7	N	Y	Y
14	M	OD	70	0.4	Y	Y	N
15	F	OS	64	0.4	Y	Y	N
16	M	OD	64	0.3	N	Y	Y
17	F	OS	74	0.5	N	Y	Y
3 risks ($n = 10$)							
1	F	OD	81	0.3	Y	Y	Y
2	M	OS	62	0.2	Y	Y	Y
3	F	OS	88	0.2	Y	Y	Y
4	F	OD	64	0.3	Y	Y	Y
5	F	OS	64	0.3	Y	Y	Y
6	F	OS	81	0.5	Y	Y	Y
7	M	OS	89	0.4	Y	Y	Y
8	M	OD	64	1.0	Y	Y	Y
9	M	OD	62	0.2	Y	Y	Y
10	M	OD	89	0.5	Y	Y	Y

BCVA = best corrected visual acuity; OD = right eye; OS = left eye.

3.1. Metabolic risks are associated with altered inner retinal thickness at the parafovea and perifovea

Patients without (0 risk) and with one or more metabolic risks (1–3 risks) were compared; no difference in age ($p = 0.063$) was observed, but the BCVA was markedly decreased in patients with metabolic risks ($p = 0.016$) (Table 3). It is known that the circulation of the inner retina is supplied by the retinal artery, while the outer retina is supplied by the choroidal artery, so we first compared the difference of the full, inner and outer retinal thickness between patients with and without metabolic risks. It was demonstrated that metabolic risks did not affect the thickness of the full retina and the outer retina at the fovea, parafovea and perifovea ($p > 0.05$); however, the thickness of the inner retina at the

Table 3
Relationship between metabolic risks and retinal thickness.

Patient numbers	Metabolic risk (−)	Metabolic risk (+)	*p*
	$n = 11$	$n = 43$	
Age (y)	66.5 ± 8.00	71.9 ± 8.50	0.063
BCVA	0.64 ± 0.169	0.46 ± 0.220	0.016*
Full retinal thickness (μm)			
Fovea	267.0 ± 28.29	257.5 ± 25.57	0.545
Parafovea	285.4 ± 18.74	286.9 ± 17.12	0.293
Perifovea	263.5 ± 13.59	264.3 ± 16.54	0.408
Inner retinal thickness (μm)			
Fovea	79.8 ± 16.64	78.3 ± 15.80	0.780
Parafovea	110.1 ± 11.79	99.2 ± 12.79	0.013*
Perifovea	100.7 ± 8.61	92.6 ± 10.19	0.018*
Outer retinal thickness (μm)			
Fovea	172.5 ± 12.93	179.3 ± 14.63	0.165
Parafovea	183.5 ± 14.49	187.0 ± 15.66	0.511
Perifovea	170.6 ± 10.32	172.5 ± 13.74	0.682

t test: * $p < 0.05$.
BCVA = best corrected visual acuity.

parafovea ($p = 0.013$) and perifovea ($p = 0.018$), rather than the central fovea ($p = 0.780$), was significantly decreased in patients with metabolic risks (Table 3).

3.2. Loss of inner retinal thickness and BCVA were responses to accumulative metabolic risks

Next, we analyzed whether accumulative metabolic risks affected the BCVA or retinal thickness. In our study, there was no significant difference in age between the zero risk, one risk, two risk, and three risk groups. The results in Table 4 demonstrated that the BCVA was marginally decreased in patients with one or two metabolic risks (level ab), and was only markedly decreased in patients with three metabolic risks (level b) (ANOVA, $p < 0.05$). As shown in Table 3, accumulative metabolic risks did not alter the full and outer retinal thickness at the entire macular area. However, for patients with one or two metabolic risks, a decrease in inner retinal thickness could be found either at the perifovea or the parafovea; for patients with three metabolic risks, a significant loss of inner retinal thickness occurred both at the parafovea (level b) and the perifovea (level b) (Table 4) (ANOVA, $p < 0.05$).

3.3. Superior inner retina was sensitive to hypertension, hyperglycemia and dyslipidemia

The inner retina was further divided into the superior, or inferior hemispheres, or the quadrisphere, based on the superior and inferior divisions of retinal artery. Analysis of the inner retinal thickness at the parafovea showed that the superior inner retina ($p = 0.013$) was more sensitive to metabolic damage than the inferior inner retina ($p = 0.059$), and a similar appearance could be observed at the perifoveal area (Table 5). In response to accumulative metabolic damage, patients with one metabolic risk showed a marginal decrease in the superior inner retinal thickness at the parafovea (level ab), while patients with two or three metabolic risks showed a significant loss of their superior inner retinal thickness at the parafovea (Table 6). In comparison to the parafovea, a loss of superior inner retinal thickness in response to accumulative metabolic damage was not remarkable at the perifovea (Table 6).

Table 5
Relationship between metabolic risks and inner retinal thickness at the parafovea and perifovea.

Patient numbers	Metabolic risk (−)	Metabolic risk (+)	*p*
	$n = 11$	$n = 43$	
Inner retinal thickness at parafovea (μm)			
Superior hemisphere	112.4 ± 13.11	99.9 ± 14.71	0.013*
Inferior hemisphere	107.7 ± 11.74	98.4 ± 14.82	0.059
Superior temporal	113.1 ± 15.63	100.5 ± 14.95	0.017*
Superior nasal	116.2 ± 14.27	101.7 ± 14.61	0.005**
Inferior temporal	103.5 ± 10.93	95.7 ± 12.97	0.070
Inferior nasal	107.7 ± 15.45	98.7 ± 18.57	0.143
Inner retinal thickness at perifovea (μm)			
Superior hemisphere	98.4 ± 10.19	90.4 ± 11.31	0.040*
Inferior hemisphere	103.3 ± 8.80	94.7 ± 13.14	0.046*
Superior temporal	95.2 ± 8.52	89.2 ± 13.19	0.090
Superior nasal	96.8 ± 12.08	99.5 ± 11.55	0.036*
Inferior temporal	107.7 ± 10.25	87.0 ± 13.48	0.063
Inferior nasal	103.3 ± 12.07	94.4 ± 13.49	0.053

t test: * $p < 0.05$; ** $p < 0.01$.

3.4. Medication controlling the metabolic risk factors did not alter the inner retinal thickness at the parafovea

For patients with one, two, and three metabolic risks, those under good medical control were defined as the well control group. Patients who received unsatisfactory medication, or who were without medication, were defined as the poor control group. Poor control groups were further divided into two or three groups depending on the uncontrolled metabolic risk numbers. Among the 16 patients with one metabolic risk, the mean inner parafovea retinal thickness of the 10 well control cases was 97.9 ± 11.17 μm *versus* 98.33 ± 17.76 μm for the six poor control cases (Fig. 3A).

Table 4
Effect of accumulative metabolic risks on best corrected visual acuity (BCVA) and inner retinal thickness.

Patient numbers	0 risks	1 risk	2 risks	3 risks
	$n = 11$	$n = 16$	$n = 17$	$n = 10$
Age (y)	66.5 ± 8.00$^{(a)}$	72.2 ± 7.52$^{(a)}$	70.1 ± 6.78$^{(a)}$	74.4 ± 12.16$^{(a)}$
BCVA	0.64 ± 0.150$^{(a)}$	0.47 ± 0.227$^{(ab)}$	0.49 ± 0.203$^{(ab)}$	0.39 ± 0.242$^{(b)}$
Full retinal thickness (μm)				
Fovea	267.0 ± 28.29$^{(a)}$	267.0 ± 28.29$^{(a)}$	250.8 ± 23.69$^{(a)}$	253.9 ± 21.42$^{(a)}$
Parafovea	285.4 ± 18.74$^{(a)}$	285.4 ± 18.74$^{(a)}$	290.8 ± 13.05$^{(a)}$	282.9 ± 20.74$^{(a)}$
Perifovea	263.5 ± 13.59$^{(a)}$	263.5 ± 13.59$^{(a)}$	267.1 ± 18.45$^{(a)}$	261.1 ± 18.35$^{(a)}$
Inner retinal thickness (μm)				
Fovea	79.8 ± 16.64$^{(a)}$	86.0 ± 18.17$^{(a)}$	73.3 ± 11.83$^{(a)}$	74.5 ± 14.05$^{(a)}$
Parafovea	110.1 ± 11.79$^{(a)}$	100.5 ± 14.03$^{(ab)}$	98.6 ± 13.46$^{(b)}$	98.0 ± 10.38$^{(b)}$
Perifovea	100.7 ± 8.61$^{(a)}$	93.2 ± 8.77$^{(b)}$	92.5 ± 12.50$^{(ab)}$	91.6 ± 8.78$^{(b)}$
Outer retinal thickness (μm)				
Fovea	172.5 ± 12.93$^{(a)}$	181.1 ± 17.22$^{(a)}$	177.7 ± 14.84$^{(a)}$	179.4 ± 10.09$^{(a)}$
Parafovea	183.5 ± 14.49$^{(a)}$	185.1 ± 16.93$^{(a)}$	190.1 ± 16.02$^{(a)}$	184.8 ± 13.44$^{(a)}$
Perifovea	170.6 ± 10.32$^{(a)}$	170.4 ± 12.29$^{(a)}$	176.4 ± 15.79$^{(a)}$	169.1 ± 11.65$^{(a)}$

ANOVA with Tukey's post-hoc tests at 95% confident intervals; different characters represent different levels of significance. Comparison of retinal thickness at the same area in patients among 0, 1, 2, and 3 risks groups, level "b" represents level significantly lower than level "a", while level "ab" indicates level in between levels "a" and "b".

Table 6
Effect of accumulative metabolic risks on inner retinal thickness at the parafovea and perifovea.

Patient numbers	0 risks	1 risk	2 risks	3 risks
	$n = 11$	$n = 16$	$n = 17$	$n = 10$
Inner retinal thickness at parafovea (μm)				
Superior hemisphere	$112.4 \pm 13.11^{(a)}$	$101.0 \pm 15.46^{(ab)}$	$98.1 \pm 17.56^{(b)}$	$100.5 \pm 7.55^{(b)}$
Inferior hemisphere	$107.7 \pm 11.74^{(a)}$	$99.8 \pm 13.98^{(ab)}$	$99.0 \pm 16.19^{(ab)}$	$95.3 \pm 14.78^{(b)}$
Superior temporal	$113.1 \pm 15.63^{(a)}$	$101.1 \pm 15.74^{(ab)}$	$99.9 \pm 21.19^{(b)}$	$101.4 \pm 9.38^{(ab)}$
Superior nasal	$116.2 \pm 14.27^{(a)}$	$104.2 \pm 17.12^{(ab)}$	$100.4 \pm 14.62^{(b)}$	$99.8 \pm 10.44^{(b)}$
Inferior temporal	$103.5 \pm 10.93^{(a)}$	$97.3 \pm 11.86^{(a)}$	$95.1 \pm 14.92^{(a)}$	$94.2 \pm 12.15^{(a)}$
Inferior nasal	$107.7 \pm 15.45^{(a)}$	$99.0 \pm 15.93^{(a)}$	$99.9 \pm 21.19^{(a)}$	$96.1 \pm 19.46^{(a)}$
Inner retinal thickness at perifovea (μm)				
Superior hemisphere	$98.4 \pm 10.19^{(a)}$	$89.9 \pm 9.82^{(b)}$	$88.7 \pm 14.55^{(ab)}$	$94.3 \pm 6.11^{(ab)}$
Inferior hemisphere	$103.3 \pm 8.80^{(a)}$	$96.4 \pm 9.14^{(ab)}$	$96.5 \pm 15.56^{(ab)}$	$89.5 \pm 13.75^{(b)}$
Superior temporal	$95.2 \pm 8.52^{(a)}$	$88.4 \pm 10.66^{(a)}$	$86.7 \pm 17.18^{(a)}$	$94.9 \pm 6.98^{(a)}$
Superior nasal	$96.8 \pm 12.08^{(a)}$	$101.3 \pm 11.64^{(ab)}$	$99.2 \pm 11.65^{(ab)}$	$97.2 \pm 11.99^{(b)}$
Inferior temporal	$107.7 \pm 10.25^{(a)}$	$86.6 \pm 10.00^{(b)}$	$88.6 \pm 17.56^{(ab)}$	$85.0 \pm 11.11^{(b)}$
Inferior nasal	$103.3 \pm 12.07^{(a)}$	$96.1 \pm 11.68^{(ab)}$	$95.5 \pm 13.65^{(ab)}$	$89.9 \pm 16.15^{(b)}$

ANOVA with Tukey's post-hoc tests at 95% confident intervals; different characters represent different level of significance. Comparison of retinal thickness at the same area in patients among 0, 1, 2, and 3 risks groups, level "b" represents level significantly lower than level "a", while level "ab" indicates level in between levels "a" and "b".

In patients with two metabolic risks (17 cases), the mean inner parafovea retinal thickness of four well control cases was 92.25 ± 10.05 μm; it was 99.11 ± 16.32 μm in nine patients with one abnormal metabolic profile, and 104 ± 7.87 μm in four patients with two abnormal metabolic profiles (Fig. 3B). No one in the well medical control group was in the three risk group (10 cases); two had one abnormal metabolic profile, with an inner parafovea retinal thickness of 87.5 ± 16.26 μm, three had two abnormal metabolic profiles, with an inner parafovea retinal thickness of 96.33 ± 5.77 μm, and five had three abnormal metabolic profiles, with an inner parafovea retinal thickness of 102.6 ± 8.50 μm. Analysis of inner retinal thickness at the parafovea showed no significant difference between the well control group and the poor control group(s) ($p > 0.05$).

4. Discussion

For the first time, we demonstrated the correlation of metabolic risk factors and inner retinal thickness at the macular area. It would therefore be important to routinely measure the inner retinal

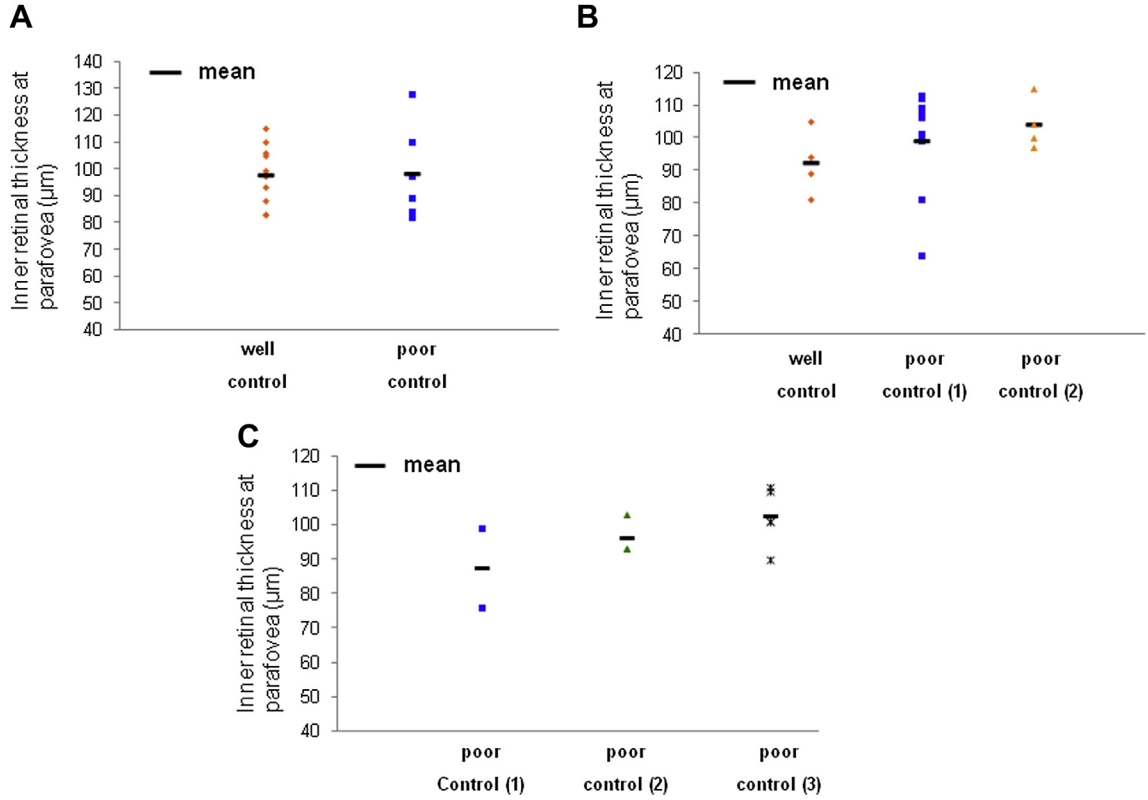

Fig. 3. Analysis of inner retinal thickness at the parafovea and impact of medical control. Among 54 patients with metabolic risks, three groups were divided by their metabolic risk factor numbers: (A) 16 patients with one metabolic risk; (B) 17 patients with two metabolic risks; and (C) 10 patients with three metabolic risks. Fig. 3A–C illustrated the individual inner retinal thickness at the parafovea. There was no significant difference in inner retinal thickness between the well control group and the poor control group(s) in patients with one, two or three risks, respectively ($p > 0.05$). The well control group was defined as patients with normal metabolic profile under medication and the poor control group (n) was defined as patients who had "n" abnormal metabolic profile(s) with or without medication.

thickness in patients with metabolic risk factors, despite negative findings under indirect fundoscopy. We found that impaired metabolic homeostasis specifically affected the inner retina, but not the outer retina, at the parafovea and perifovea, and superior inner retinal loss at the parafovea was more sensitive than inferior inner retina. The central fovea was relatively spared metabolic injury. Moreover, the severity of inner retinal loss was response to accumulative metabolic damage, which occurred earlier than visual disturbance.

It is well established that the pathophysiology of metabolic syndrome, such as hypertension, dyslipidemia, and hyperglycemia, is a vasculopathy in nature.[24–27] Patients with metabolic risk factors had an increased risk of retinopathy.[28] It has been reported that metabolic syndrome is associated with endothelial dysfunction, inflammation,[29] and impaired retinal vasculature.[26] In the human retina, the inner retina is supplied by the retinal artery, with a direct holangiotic vascular pattern, while the outer retina is supplied by numerous anastomotic choroidal vessels.[30,31] In this study, the inner retinal thickness was selectively affected by impaired metabolic homeostasis (Table 3), suggesting that the retinal artery is more sensitive to metabolic abnormality than the choroidal artery. Different from retinal circulation, choroidal circulation constantly keeps a high blood flow to protect eye tissues from thermal injury and to regulate retinal oxygenation.[32] This may explain why choroidal vessels are relatively more resistant to metabolic problems. Therefore, the change of inner retinal thickness was one of the sequelae of impaired metabolic homeostasis that manifested prior to retinal hemorrhage, vascular leakage, narrowing of the artery, and vascular occlusion.

In this study, the number of metabolic risk factors was associated with the progression of inner retina loss at the parafovea and perifovea (Table 4). Apoptosis of retinal neuroglial tissue, especially at the parafovea, occurred in the early phase of diabetic retinopathy and was associated with impaired retinal function.[19–21] Retinal neuroglial cells at the parafovea were the most abundant, with the greatest thickness in the retina. In the current study, we demonstrated that in hyperglycemic patients without diabetic retinopathy, and in patients with hypertension or dyslipidemia, loss of inner retinal thickness at the parafovea and perifovea can also be observed (Table 3). Compared to superior and inferior inner retinal thickness, we found that the selective superior hemisphere at the parafovea and both the superior and inferior hemisphere at the perifovea were affected by metabolic injury (Table 4), indicating that the metabolic syndrome-related microvascular change in the superior branch of the retinal artery induced an initial loss of neuroglial cells in the inner retina.

It was noteworthy that in the inner retina, at the macular area, the central fovea (Fig. 1) was spared metabolic injury, and visual disturbance was not significant, except in patients with three metabolic risks (Table 3). We suggested that the fovea was insensitive to the chronic change of retinal microvascular abnormalities, which might be contributed to by avascular characteristics and the lack of inner retinal layer at the central fovea.

In this study, 17 of 24 hypertensive patients, 25 of 28 dyslipidemic patients and 22 of 28 hyperglycemic patients had the other one or two metabolic risks (Fig. 2), which illustrated that concomitant hypertension, dyslipidemia and hyperglycemia are very common. Additionally, the association between dyslipidemia and hypertension or hyperglycemia was relatively high (Fig. 2C). The mechanisms of how metabolic risk factors interacted with each other and regulated the inner retinal thickness at the parafovea and perifovea should be further investigated.

We also found that inner retinal thickness at the parafovea did not correlate to medical control of metabolic risks. The irreversible damage of retinal neuron degeneration may one of the explanations for our finding. The limited number of cases, as well as mislabeling a patient who had a fluctuating blood sugar level as being in the well control group, may also affect the interpretation in this study.

There were some limitations of our study due to the limited sample size: (1) the effects of medications for controlling metabolic risk factors; (2) the duration or severity of hypertension, dyslipidemia, or hyperglycemia on retinal thickness; (3) factors other than metabolic risks may affect the blood supply of the retina. The relationship between the severity of metabolic syndrome and macular degeneration warrants a further large-scale longitudinal investigation in the future.

It is well established that the severity of diabetic nephropathy was associated with a worsening of diabetic retinopathy.[33] In this study, we observed a positive correlation between accumulative metabolic risks and the severity of abnormal serum creatinine levels in some patients (3 patients had an abnormal serum creatinine level in the 2 risk group, 1 patient had received hemodialysis in the 3 risk group), but the relationship between abnormal serum creatinine level and retinal thickness could not be concluded, due to the limited number of cases.

Taken together, there was a significant decrease in inner retinal thickness at the parafovea and perifovea in patients with metabolic risk factors, while the fovea was relatively resistant to metabolic injury. The severity of inner retina loss was associated with the accumulated metabolic risk factors. Visual impairment induced by metabolic abnormality was less sensitive than inner retina loss at the perifovea and parafovea. Thus, measurement of inner retinal thickness at the macular area was indispensable for a patient with metabolic risk factors, but negative for retinopathy.

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