Beyond Hyperglycemia, Evidence for Retinal Neurodegeneration in Metabolic Syndrome

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PURPOSE. We evaluated the retinal effects of systemic metabolic changes clustered under the umbrella of metabolic syndrome (MetS) in comparison with age-matched healthy subjects.

METHODS. Spectral-domain optical coherence tomography (OCT) retinal segmentation analysis of 29 patients with MetS and 36 control subjects was performed. Patients with diabetes mellitus (DM), uncontrolled hypertension, retinopathy, high myopia or hyperopia, and posterior segment surgery, were excluded from analysis. The control group (CG) was selected from age- and sex-matched healthy lean subjects. Mean thickness values of individual retinal layers in nine macular early treatment of diabetic retinopathy study (ETDRS) subfields were determined.

RESULTS. The MetS group had a significantly thinner ganglion cell layer in two (MetS, 52.4 ± 5.1 μm; CG, 54.8 ± 3.8 μm; P = 0.030), thinner inner plexiform layer in three (MetS, 39.8 ± 4.4 μm; CG, 43.0 ± 3.5 μm; P = 0.003), thinner photoreceptor layer in seven (MetS, 79.4 ± 2.9 μm; CG, 81.1 ± 2.9 μm; P = 0.009) of nine ETDRS subfields. No difference was found in nerve fiber, inner nuclear, outer plexiform, and outer nuclear layers.

CONCLUSIONS. The patients with MetS had thinner inner retinal layers and photoreceptor layer in OCT segmentation analysis, which suggests that inherent factors of MetS, such as insulin resistance and adipose tissue-derived inflammation, might have a neurodegenerative effect independent of the hyperglycemic levels associated with DM. Therefore, beyond glycemic control measures, weight reduction also might be advised to overweight patients with type 2 DM and MetS to prevent the occurrence of retinal neurodegeneration.

Keywords: diabetes mellitus, insulin resistance, metabolic syndrome, optical coherence tomography, retinal segmentation, retinal neurodegeneration

Metabolic syndrome (MetS) is the co-occurrence of a group of major cardiovascular disease (CVD) risk factors, such as abdominal obesity, high fasting blood glucose, high blood pressure, and dyslipidemia. MetS increases the incidence of CVD and all-cause mortality rates similar to diabetes mellitus (DM).¹ It has a very high prevalence of 20% to 25% in the world adult population, making it the major driving force for development of the new CVD epidemic.²

Individuals with MetS have a 5-fold increased risk for the development of DM, which is a worldwide pandemic disease with an estimated increased prevalence from 2.8% in 2000 to 4.4% in 2030 for all age-groups, doubling the number of people at risk for vision loss.³ DM causes a series of macrovascular (ischemic heart disease, CVD, and peripheral vascular disease) and microvascular (retinopathy, nephropathy, and neuropathy) complications resulting in significant morbidity and mortality. Diabetic retinopathy (DRP) has a complex pathophysiology in which various mechanisms act together to produce common clinical signs and symptoms. DM also has been shown to produce retinal neurodegenerative changes in optic coherence tomography (OCT) and multifocal electroretinography (ERG) studies even many years before the onset of nonproliferative DRP.⁴,⁵ Hyperglycemia is the major long-term determinant of retinal changes observed in DRP. Its role has been confirmed in The Diabetes Control and Complications Trial where intensive glycemic control has been shown to prevent the development and delay the progression of DRP in a cohort of patients with type 1 DM.⁶⁻⁸ However, the efficiency of intensive glycemic control is more equivocal in patients with type 2 DM. It has been shown to provide benefit in some studies and contradicting results were present in the others.⁹⁻¹³ This reduced efficacy of glycemic control in patients with type 2 DM (21% vs. 76% reduction in DRP progression in type 2 vs. type 1 DM, respectively) suggests that different mechanisms other than hyperglycemia might have an effect in the development of DRP. Although the diagnosis of DM has clear-cut definitions, many patients experience an abnormal hyperglycemic state named as prediabetes before the development of overt DM.¹⁴,¹⁵ In this prediabetic period, some patients undergo a series of metabolic changes, namely the components of the MetS, which affect the cardiovascular and metabolic state of the individual for many years before onset of frank DM. Although, type 2 DM frequently is associated with MetS, MetS also can be seen as an isolated entity without the presence of frank DM, which provides an opportunity to study the retinal degenerative effects of the associated systemic changes beyond diabetic level hyperglycemia. To investigate the retinal degenerative effects of the systemic mechanisms other than hyperglycemia in a controlled manner, we systematically analyzed the individual retinal layers of patients with MetS with the spectral domain OCT retinal
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Materials and Methods

This was a cross-sectional study, done at the Erciyes University School of Medicine Department of Ophthalmology and Endocrinology. The study followed the Declaration of Helsinki and approved by the institutional review board. Written informed consent was obtained from all subjects. All study participants were reviewed for ocular and medical history. They were excluded if they had DM, diabetic retinopathy, diabetic macular edema, retinal vein occlusion, intra vitreal injections, focal or grid laser treatment, macular degeneration, previous photodynamic therapy (PDT), myopia of more than 6 diopters (D) or axial length more than 26.5 mm, posterior segment surgery including vitrectomy or scleral buckling, amblyopia, glaucoma, ocular hypertension, or uncontrolled hypertension. All subjects had full ophthalmologic examination, including best corrected visual acuity determination, slit-lamp biomicroscopy, dilated fundus examination, IOP measurement, axial length measurement by the Nidek Optical Biometer AL Scan instrument (Nidek Co. Ltd., Aichi, Japan) and OCT imaging. Right eyes of each subject were used for data analysis.

MetS group patients were recruited from the Erciyes University Department of Endocrinology and Metabolism based on the revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III guideline. The diagnosis of the MetS was based on the presence of three of the following five risk factors:16,17 fasting plasma glucose higher than 110 mg/dL, were excluded from analysis.18

Control group (CG) subjects were selected among age- and sex-matched, healthy, lean individuals. CG subjects were screened for the presence of MetS and DM. Fasting plasma glucose, serum triglycerides, HDL levels were determined, and blood pressure and waist circumference were measured. Subjects with MetS, history of DM, hypertension, or fasting plasma glucose higher than 110 mg/dL, were excluded from analysis.

OCT Imaging

OCT images were obtained with the Heidelberg Spectralis OCT machine (Heidelberg Engineering GMBH, Heidelberg, Germany) after pupillary dilation, by a single experienced technician. Fast macular thickness OCT protocol was used with 20° × 20° raster scans. Each scan consisted of 25 linear scans with nine frames per B scan in automatic real-time function setting. Good quality scans with signal strength >20 (maximum = 40) were accepted for analysis. Low quality scans with misalignment, defocus, blank areas, or artefacts were excluded from analysis. An internal fixation target was used for foveal centration with an active eye tracker.

Image analysis was performed with built-in automatic retinal segmentation software (HRA/Spectralis viewing module 6.8.1.0). Retinal segmentation analysis was performed to obtain individual retinal thickness measurements, including retinal nerve fiber layer (RNFL), inner plexiform layer (IPL), inner nuclear layer (INL), inner retinal layers (between internal limiting membrane and outer plexiform layer, IRL), outer nuclear layer (ONL), photoreceptor layer (between external limiting membrane and Bruch membrane, PRL), RPE, and overall retinal thickness (RT; Fig. 1). An Early Treatment Diabetic Retinopathy Study (ETDRS) plot consisting of three concentric 1-, 3-, and 6-mm diameter rings centered over the fovea was projected onto the retina.19 The two outer rings were divided into four quadrants by two intersecting lines generating nine subfields in total (central [C], nasal [N], superior [S], temporal [T], inferior [I], peripheral nasal [pN], peripheral superior [pS], peripheral temporal [pT], peripheral inferior [pI]; Fig. 2). OCT images were assessed by an examiner (CK) masked to the group of the patient. Centralization of the ETDRS plot over foveal center was checked and corrected if decentration was detected. Mean thickness values of each retinal layer in nine ETDRS subfields were recorded (Fig. 2).

Statistical Analysis

Statistical analysis was performed using the SPSS Version 22 (IBM, Inc., Chicago, IL, USA) program. The normal distribution of the data was tested with the Shapiro-Wilk test. Comparisons between the groups were done with two independent samples t-tests, and Mann–Whitney U tests where appropriate. Comparisons between categorical variables were done with the χ² square test. Data were expressed as mean ± SD. A P value lower than 0.05 was considered statistically significant.

Results

The study groups consisted of 29 eyes of 29 patients with MetS and 36 eyes of 36 healthy age- and sex-matched control subjects. Age and sex distribution of the subjects were similar between the study groups (Table 1). The CG had lower fasting blood glucose (CG, 88.6 ± 9.1 mg/dL vs. MetS, 96.6 ± 10.3 mg/dL; P = 0.002), higher serum HDL (53.7 ± 12.5 vs. 40.7 ± 10.1 mg/dL, respectively; P < 0.001), and lower triglyceride (104.6 ± 43.0 vs. 228.3 ± 81.0 mg/dL, respectively; P < 0.001) levels compared to the MetS group. The waist circumference was significantly shorter in the CG than in the MetS group (85.8 ± 8.5 vs. 94.6 ± 10.4 cm, respectively; P < 0.001; Table 1).

The MetS group had a significantly thinner ganglion cell layer (GCL) in two of four subfields of the 3-mm ETDRS circle (C, 47.2 ± 4.9 µm for MetS vs. 49.7 ± 4.3 µm for CG; P = 0.039; I, 52.4 ± 5.1 vs. 54.8 ± 3.8 µm, respectively; P = 0.030); thinner IPL in three of four subfields of the 3-mm ETDRS circle (N, 41.6 ± 3.4 vs. 44.1 ± 3.5 µm, respectively; P = 0.014; T, 40.4 ± 4.2 vs. 42.6 ± 3.4 µm, respectively; P = 0.049; I, 39.8 ± 4.4 vs. 43.0 ± 3.5 µm, respectively; P = 0.003); thinner PRL in the central 1 mm in four of four subfields of the 3-mm and two of four subfields of the 6-mm ETDRS circles (C, 86.4 ± 4.2 µm vs. 88.9 ± 3.9 µm, respectively; P = 0.013; N, 79.4 ± 2.9 vs. 81.1 ± 2.9 µm, respectively; P = 0.009; S, 78.3 ± 2.9 vs. 80.3 ± 2.7 µm, respectively; P = 0.004; I, 77.2 ± 2.3 vs. 78.6 ± 2.0 µm, respectively; P = 0.006; pN, 75.9 ± 2.1 vs. 77.2 ± 2.4 µm, respectively; P = 0.015; pS, 76.5 ± 2.0 vs. 78.2 ± 2.5, respectively; P = 0.008); thinner RPE layer in two of four subfields of the 6-mm ETDRS circle (pN, 12.8 ± 1.3 vs. 13.6 ± 1.2 µm, respectively; P = 0.020; pS, 13.5 ± 1.2 vs. 14.1 ± 1.1 µm, respectively; P = 0.009); thinner IRL in two of four
subfields of the 3-mm ETDRS circle (T, 247.1 ± 13.7 vs. 253.3 ± 10.8 μm, respectively; \( P = 0.048 \); I, 259.5 ± 15.7 vs. 267.2 ± 11.6 μm, respectively; \( P = 0.026 \)); and global thinning of the retina was observed in the central 1 mm in three of four subfields of the 3-mm ETDRS circle (C, 265.1 ± 18.7 vs. 274.5 ± 18.2 μm, respectively; \( P = 0.047 \); N, 342.0 ± 16.2 vs. 350.4 ± 12.5 μm, respectively; \( P = 0.021 \); T, 325.7 ± 14.2 vs. 333.8 ± 12.0 μm, respectively; \( P = 0.015 \); I, 336.7 ± 16.3 vs. 346.0 ± 12.1 μm, respectively; \( P = 0.011 \); Figs. 3, 4; Table 2).

No correlation was found between mean thickness values of thinned retinal layers (GCL, IPL, and PRL) and MetS parameters (triglyceride, high-density lipoprotein [HDL] cholesterol, waist circumference, blood pressure, and glucose levels).

Four patients in the MetS group were on antihypertensive treatment (two calcium channel blockers, one calcium channel blocker-angiotensin receptor blocker, one diuretic-angiotensin converting enzyme inhibitor). Two patients in the MetS group...
and two in the CG received levothyroxine for hypothyroidism; they all were euthyroid under levothyroxine therapy.

**DISCUSSION**

In this study, we found that patients with MetS had evidence for the presence of retinal neurodegeneration. Its presence was demonstrated by thinning of the overall retinal thickness compared to the CG. The changes were caused primarily by thinning of the IRLs namely the GCL, IPL of the 3-mm ETDRS ring, and thinning of the PRL of the 5- and 6-mm ETDRS rings (Figs. 3, 4; Table 2). DRP has long been considered as a microangiopathy causing microvascular changes, such as leakage and capillary occlusion. However, retinal neurodegenerative changes have been shown to precede the development of nonproliferative DRP in morphologic OCT and electrophysiologic testing. Thinning of IRLs (GCL-IPL complex and RNFL) and, or photoreceptor layer (ORL) has been found to be present in OCT studies done on patients with types 1 and 2 DM.5,20–23 Thickening of the INL also has been reported in types 1 and 2 DM.24,25 The activation and swelling of the Müller cells to compensate for extracellular accumulation of fluid with subclinical macular edema was held responsible for the thickening in early DM. The neurodegeneration pattern found in our MetS group was similar to the neurodegeneration pattern described in previous studies done on DM subjects without DRP and no evidence of subclinical macular edema. The association of MetS and retinopathy in patients without a history of diabetes has been researched in a number of studies.26–30 A positive correlation was found between MetS or its components and development of retinopathy, which was identified by detection of funduscopic abnormalities, such as microaneurysms, retinal hemorrhages and so forth. In contrast, our study was performed with OCT providing a more sensitive analysis and quantitative data. Recently, neurodegeneration has been found in a study done on a group of prediabetic subjects based on the criteria proposed by American Diabetes Association.31 The analysis was restricted to the peripapillary RNFL and macular GCL, where thinning was found. However, in that study only eight of 30 patients had the diagnosis of MetS, and a separate analysis for patients with MetS was not performed. As MetS definition encompasses broader metabolic changes, including but not limited to disturbed glucose metabolism, our study has the advantage of analyzing the retinal effects of a more globally affected metabolic state, with a more detailed retinal segmentation analysis (peripapillary RNFL, GCL analysis versus whole retinal segmentation analysis).

In this study, we found that patients with MetS had neurodegeneration similar to those with DM with no evidence of DRP.5,20–23 This neurodegeneration can be caused by a
variety of factors, the most important factor of which is hyperglycemia as neurodegeneration also can be seen in patients with type 1 DM. However, mechanisms other than hyperglycemia should be present as the patients with MetS do not have diabetic level hyperglycemia and patients with type 2 DM have a reduced protective response to glycemic control measures. Evidence for the presence of other factors has been shown in a study done on adolescent patients with types 1 and 2 DM.20 In that study, mean retinal thickness of the type 1 DM group was not different from the CG. However, mean retinal thickness of patients with type 2 DM was significantly thinner despite the presence of a shorter disease duration in these patients (2.1 \pm 1.3 years) compared to those with type 1 DM (5.7 \pm 3.6 years). The investigators suggested several inherent factors of type 2 DM rather than hyperglycemia to be responsible for the difference.20

Insulin resistance (IR), the hallmark of MetS and type 2 DM, can be one of these factors. In IR states, the ability of insulin to influence glucose uptake via insulin-dependent glucose transporters is impaired. A higher-than-normal insulin concentration is required to maintain normal glucose levels. In fact, IR, namely the brain-specific IR, has been implicated as an important pathophysiologic mechanism in the development of a serious central nervous system neurodegenerative disorder, namely Alzheimer’s disease (AD).32,33 The prevalence of diabetes or prediabetes is approximately 81% in patients with AD in the United States where peripheral IR is accompanied with or without type 2 DM.54 AD is a chronic
progressive neurodegenerative disorder that is believed to start many years before the signs and symptoms of cognitive dysfunction become manifest. Functional insulin signaling and downstream elements of the insulin signaling pathway have been shown to be required for neuronal cell survival, to facilitate synaptic plasticity, and to be implicated in the link between IR and AD. Beyond AD, IR also has been implicated to have a role in the pathophysiologic mechanisms of several neurodegenerative disorders, such as Huntington’s disease, Parkinson’s disease (PD), depression, and schizophrenia sharing features of neuro-inflammation and neurodegeneration.39

Low grade systemic inflammation and neuro-inflammation can be another explanation for the development of neurodegeneration. Neuro-inflammation is an inherent defense mechanism of the nervous system against injuries and infections protecting and restoring its normal functioning. Neuro-inflammation is linked closely with neurodegenerative processes in which activated glial cells secrete several cytokines, chemokines, and reactive oxygen species (ROS), which culminate in cellular injury resulting in diseases, such as AD, PD, and multiple sclerosis.36 Peripheral inflammation is shown to exacerbate the neuro-inflammatory responses in the central nervous system (CNS).37 Neurodegenerative disorders are associated with increased plasma levels of inflammatory markers, such as IL-6, TNF-α, and chemokine (C-C motif) ligand 2 (CCL2).37 Increased peripheral inflammation increases blood–brain barrier (BBB) permeability. Disruption of the BBB increases the immune cell and inflammatory molecule flow across the BBB, thereby augmenting the neuro-inflammation.38 Mets and type 2-DM usually are associated with a dysfunctional adiposity. Increased caloric intake and developing obesity is characterized by an undesired toxic ectopic lipid accumulation with increased triglycerides, which is located predominantly in the trunk area. This abnormal adipose tissue is associated with dysfunctional adipokine release (e.g., increased TNF-α, IL-6, leptin, decreased adiponectin) and elevated serum C-reactive protein levels.39 Increased TNF-α and leptin stimulate the release of monocytic chemotactic protein (MCP-1). Increased MCP-1 causes adhesion and infiltration of adipose tissue with macrophages resulting in a

Table 2. Continued

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<tr>
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<td>Peripheral inferior</td>
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<td>RPE thickness, μm</td>
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<td>Peripheral inferior</td>
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Statistically significant P values are represented in bold.
generation of a toxic inflammatory environment. This dysfunctional adipose tissue–originated chronic low grade systemic inflammation can be a factor in the development of retinal neurodegeneration in MetS and type 2 DM. Increased triglyceride levels were reported to be associated with increased INL thickness in type 1 DM subjects with early retinal degeneration. Moreover, fenofibrate (FA) therapy was shown to lower the progression of DRP by reducing triglyceride levels in type 2 DM subjects. However, the protective effect of FA was reported to be independent of its lipid-lowering effects. FA is hypothesized to suppress apoptosis, stimulate endothelial nitric oxide production, and reduce systemic inflammation by modulation of tumor necrosis-α mediated inflammatory responses.

Hypertension, one of the major components of MetS, also might have an effect on the development of neurodegeneration. It is an established risk factor for the development of macrovascular and microvascular complications, such as atherosclerosis, aneurysms, and retinopathy and nephropathy, respectively. Although hypertensive and diabetic retinopathies share endothelial damage as a common underlying pathophysiologic mechanism, the damage of hypertension is primarily mechanical rather than metabolic, which makes it an unlikely explanation for the development of neurodegeneration. The antihypertensive therapy or levothyroxine treatment in MetS and CGs are not expected to affect retinal thickness analysis.

In this study, we found the patients with MetS have inner and outer retinal thinning on OCT segmentation analysis. As the inner retina is part of the central nervous system, the neurodegeneration may reflect the changes occurring in the brain caused by previously mentioned disturbed mechanisms of MetS. The macula has one of the highest metabolic rates per tissue weight in the human body. The photoreceptors have a large number of mitochondria, which is primarily located in the ellipsoid part of inner segments. Mitochondria use a high amount of oxygen to produce energy. However, 0.4% to 4% of consumed oxygen is reduced incompletely, generating ROS, which can interact with mitochondrial DNA, lipids, enzymes, and proteins to cause mitochondrial dysfunction. The imbalance between the energy intake and use, abdominal obesity, insulin resistance and, low-grade systemic inflammation might increase the ROS formation reducing the mitochondrial biogenesis, causing it to have a pivotal role in aging, obesity and the pathophysiology of various disorders, such as type 2 DM, AD, and cancer. This reduced mitochondrial biogenesis might be a factor for the increased susceptibility of the photoreceptor layer for the neurodegenerative effects of the MetS.

Our study may have some limitations. Although insulin resistance is a significant component of the metabolic syndrome, we did not directly evaluate its presence as the aim of our study was to investigate the retinal status in MetS. However, 45% of MetS group patients had high blood glucose compared to 11% in the CG. As MetS is a culmination of a myriad of mechanisms, the investigation of retinal effects of IR might require selection of a predetermined insulin-resistant patient group. The disease duration of patients with MetS can be a factor to affect the retinal segmentation analysis and classification of these patients based on disease duration might have provided more insight. However, MetS is a culmination of a myriad of several disorders having common pathophysiologic mechanisms, which take many years to become manifest. Therefore, even the newly diagnosed MetS cases may have a significant disease duration to have a retinal neuro-degenerative effect.

In conclusion, we found that patients with MetS had thinning of the IRL, including GCL and IPL, along with thinning of the photoreceptor layer in OCT segmentation analysis, which suggests that inherent factors of MetS, such as IR and dysfunctional adipose tissue–derived inflammation, might have a neurodegenerative effect independent of the hyperglycemic levels associated with DM. Therefore, beyond glycemic control measures, weight reduction also may be advised for overweight diabetic and patients with MetS with abnormal fat distribution to decrease retinal and possible CNS neurodegeneration secondary to adipose tissue–derived inflammation or neuronal insulin resistance.

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References