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The evaluation of retinal nerve fiber layer thickness in subjects with insulin resistance

İnsülin rezistansı bulunan bireylerde retina sinir lifi tabakası kalınlığının değerlendirilmesi

Feyzahan Uzun, Hüseyin Fındık, Hatice Beyazal Polat

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Abstract

Purpose: To measure the retinal nerve fiber layer thickness (RNFLT) in prediabetic subjects who were diagnosed with insulin resistance and to compare with healthy controls.

Materials and methods: A standard ophthalmological examination including measurement of best corrected visual acuity and intraocular pressure, anterior segment biomicroscopy and funduscopy was performed. Average and four quadrant (superior, temporal, inferior, nasal) RNFLT measurements were performed using spectral domain optical coherence tomography (OCT). Plasma fasting insulin and glucose levels were noted and homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated.

Results: A total of 37 patients with insulin resistance and 41 healthy controls were included in the study. Mean age of the insulin resistant group and healthy controls were 35.7±9.8 and 34.9±10.7 years, respectively. The average (95.03±11.38 µm vs 99.2±19.73 µm), inferior (119.11±18.27 µm vs 127.5±21.03 µm) and temporal (72.13±12.52 µm vs 79.2±15.97 µm) quadrant RNFL were significantly thinner in subjects with insulin resistance as compared with healthy controls (p<0.05). No significant difference was observed between the groups in the superior (121.01±9 µm vs 123.9±01 µm) and nasal (72.03±13.65 µm vs 74.52±10.52 µm) quadrants (p>0.05).

Conclusion: Despite there is lack of clinical findings in prediabetic stage, neurodegeneration of the retina may begin in the insulin resistance stage. OCT is a useful tool both in the early diagnosis and follow-up of retinal neurodegeneration.

Key Words: Diabetes mellitus, insulin resistance, optical coherence tomography.

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Özet

Amaç:İnsülin rezistansı tanısı ile takip edilen prediabetik bireylerde retina sinir lifi kalınlığının (RSLK) ölçümü ve sağlıklı kontrollerle karşılaştırılması.

Gereç ve yöntem: En iyi düzeltilmiş görme keskinliği, göz içi basıncı, ön segment ve fundus muayenelerini içeren tam oftalmolojik inceleme yapıldı. RSLK spectral-domain optik koherans tomografi (OKT) ile ölçüldü. Açlık plazma glikoz ve insülin seviyeleri not edildi ve insülin rezistans indeksi (HOMA-IR) değeri hesaplandı.

Bulgular: İnsülin rezistansı tespit edilen 37 birey ile 41 sağlıklı kontrol çalışmaya dahil edildi. Yaş ortalaması insülin rezistansı ve kontrol grubunda sırasıyla 35,7±9,8 ve 34,9±10,7 yıl idi. İnsülin rezistansı olan grupta ortalama (95,03±11,38 µm vs 99,2±19,73 µm), inferior (119,11±18,27 µm vs 127,5±21,03 µm) ve temporal (72,13±12,52 µm vs 79,2±15,97 µm) kadranlarda RSLK değeri kontrol grubuna göre istatistiksel olarak anlamlı derecede ince tespit edildi (p<0.05). Superior (121,01±9 µm vs 123,9±01 µm) ve nazal (72,03±13,65 µm vs 74,52±10,52 µm) kadranlarda anlamlı bir değişiklik saptanmadı (p>0,05).

Sonuç: Prediabetik hastalarda klinik olarak herhangi bir bulgu vermese de retina sinir lifi tabakasında nörodejenerasyon insülin rezistansı evresinde başlayabilmektedir. OKT prediabetik bireylerde erken retinal nörodejenerasyon tanısı ve takibi için uygun bir araçtır.

Anahtar Kelimeler: Diabetes mellitus, insülin direnci, optik koherans tomografi.

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Feyzahan Uzun, MD. Recep Tayyip Erdogan University, Department of Ophthalmology RİZE, e-mail: feyzahan@gmail.com (orcid.org/0000-0002-3050-0714) (Sorumlu yazar)

Hüseyin Fındık, MD. Recep Tayyip Erdogan University, School of Medicine, Department of Ophthalmology, RİZE, e-mail: drhfndk@hotmail.com (orcid.org/0000-0001-7343-8757)

Hatice Beyazal Polat, MD. Recep Tayyip Erdogan University, School of Medicine, Department of Internal Medicine, RİZE, e-mail: drpolat53@hotmail.com (orcid.org/0000-0002-7947-6874)

Introduction

Diabetic retinopathy (DR), one of the major microvascular complications of diabetes mellitus, is an important health concern worldwide. Although the exact pathophysiological mechanism is still unclear, DR is primarily believed to occur as a result of glucose-mediated vascular damage and overproduction of harmful metabolites triggered by hyperglycemia [1]. Besides, previous experimental studies showed neuronal changes including loss of ganglion cells, neural apoptosis, glial reactivity and degeneration of inner nuclear layers in the diabetic retina [2]. Whether these two aspects of DR, glucose-mediated vascular changes and retinal neurodegeneration, are in a cause-effect relationship or independent phenomena is unknown [3]. Recently a number of clinical studies have reported the evidence of retinal neurodegeneration to confirm the histopathological results from animal models of diabetes. Loss of inner retinal layer thickness and retinal degeneration was showed in diabetic patients with or even without DR [4-6].

Insulin plays an important role in retinal ganglion cell survival by exhibiting anti-apoptotic and anti-inflammatory activity, inhibiting glial activation, glutamate excitotoxicity and oxidative stress [7]. Insulin resistance (IR), a condition in which the cells become resistant to the effects of insulin, is a major risk factor for the development of diabetes and DR [8, 9]. IR was found to cause neuroinflammation and have a role in the pathophysiological mechanisms of some neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis and schizophrenia [10]. In recent clinical studies, beyond hyperglycemia, IR itself was shown to cause retinal nerve fiber layer thinning and ganglion cell loss in patients with metabolic syndrome [11, 12].

The first clinically detectable lesions of DR are vascular changes such as microaneurysms, hard exudates, cotton wool spots and intraretinal hemorrhages. However, the retinal neurodegenerative changes that occur at early phases of disease can not be detected by standard ophthalmological examination [5]. Optical coherence tomography (OCT) provides important clinical data for understanding the disorders of retina and with advances in spectral domain OCT technology even to obtain high quality segmental sections of retina and retinal nerve fiber layer with excellent repeatability and reproducibility has been possible. OCT is a useful and easily accessible tool in daily practice to detect the structural degeneration of retinal nerve tissue that occurs prior to clinically appearant functional neurovisual impairments. In this study, we aimed to investigate whether IR affects the retinal nerve structure by measuring retinal nerve fiber layer thickness in subjects with no clinically detectable ocular findings and to compare these results with healthy controls.

Materials and methods

In this prospective comparative study, included were all patients who diagnosed to have insulin resistance during the study period; a similar number of healthy individuals with similar age were included as controls. All subjects were informed about the goals of the study and informed consent was obtained. This study followed the tenets of the Declaration of Helsinki and the protocol was approved by the local Ethics Committee.

Each subject was underwent a standard ophthalmological examination including measurement of best-corrected visual acuity (BCVA) and intraocular pressure, anterior segment biomicroscopy and fundoscopy.

Exclusion criteria included any corneal or retinal abnormalities, optic disc disorders and cup/disc ratio abnormalities, any history of ocular surgery or ocular trauma, intraocular pressure higher than 21 mmHg in either eye any systemic disease which may affect retina or optic nerve (e.g. hypertension, diabetes mellitus, neurological diseases, ocular inflammatory diseases), myopia or hyperopia >2.0 diopters.

Plasma fasting insulin and glucose levels were noted for each individual and subjects whose homeostasis model assessment of insulin resistance index (HOMA-IR) [fasting insulin (μU/mL)×fasting glucose (mmol)/22.5)] value ≥2.7 were accepted to have insulin resistance.

The peripapillary RNFLT measurements were performed with a Cirrus HD spectral domain OCT (Carl Zeiss Meditec, Dublin, CA) by the same masked technician. The peripapillary RNFLT of the temporal, nasal, inferior and superior quadrants and the average thickness

of the RNFLT were obtained with the optic disc 200x200 cube scan protocol along a circle with a diameter of 3.45 mm around the center of the disc. Signal strengths >7 were included in the study.

Statistical Analysis

OCT measurements from the right eyes were used for statistical purposes. Data analysis was performed by using SPSS for Windows, version 23 (IBM Corp., Armonk, NY, USA). Whether the distribution of continuous variables was normally or not was determined by Kolmogorov Smirnov test and this test yielded normal distribution for all groups (p>0.05). Continuous variables were shown as mean ± standard deviation (SD). The mean difference between groups was compared by using Student's t test. A p value less than 0.05 was considered statistically significant.

Results

A total of 37 patients with insulin resistance and 41 healthy controls were included in the study. Mean age of the subjects who were diagnosed with insulin resistance and healthy controls were 35.7±9.8 and 34.9±10.7 years, respectively. No significant difference was observed between two groups in terms of age and gender. Metabolic parameters such as plasma fasting glucose, plasma insulin, body mass index and HOMA-IR values were significantly higher in the insulin resistant group. Table 1 shows patient demographics and baseline characteristics by groups.

The average (95.03±11.38 µm *vs* 99.2±19.73 µm), inferior (119.11±18.27 µm *vs* 127.5±21.03 µm) and temporal (72.13±12.52 µm *vs* 79.2±15.97 µm) quadrant RNFL were significantly thinner in subjects with insulin resistance as compared with healthy controls (p<0.05). No significant difference was observed between the groups (insulin resistant group *vs* control group) in the superior (121.01±9 µm *vs* 123.9±01 µm) and nasal (72.03±13.65 µm *vs* 74.52±10.52 µm) quadrants (p>0.05). Table 2 summarizes the RNFLT by groups.

Table 1. Patient demographics and baseline characteristics.

	IR group (N=37)	Control group (N=41)	*P* value
Age (years)	35.7±9.8	34.9±10.7	0.41
Gender (M:F)	6:31	8:33	0.55
BMI (kg/m²)	31.13±7.1	25.47±5.7	0.23
Fasting plasma glucose level (mmol/l)	97.9±6.8	88.5±8.4	<0.001
Plasma insulin level (µU/ml)	18.1±5.9	6.9±2.1	<0.001
HOMA-IR	4.1±1.5	1.47±0.8	<0.001

IR: Insulin resistance, M: Male, F: Female, BMI: Body mass index, HOMA-IR: Homeostasis model assessment of insulin resistance index.

Table 2. The comparison of the RNFLT between insulin resistant and control group.

RNFLT (µm)	IR Group (N=37)	Control Group (N=41)	*P* value
Average	95.03±11.38	99.2±19.73	0.003
Superior	121.01±9	123.9±01	0.53
Nasal	72.03±13.65	74.52±10.52	0.19
Inferior	119.11±18.27	127.5±21.03	<0.001
Temporal	72.13±12.52	79.2±15.97	0.0018

RNFLT: Retinal nerve fiber layer thickness, IR: Insulin resistance.

Discussion

In this study, we observed that subjects with IR had the evidence for the existance of retinal degeneration. The average, inferior and temporal quadrant RNFL were significantly thinner in subjects with IR as compared with healthy controls.

Hyperglycemia has been proposed as a major risk factor in diabetic microvascular complications such as retinopathy and neuropathy. However retinal neurodegeneration may occur even in the absence of clinically visible retinal microvascular abnormalities and the pathophysiological relationships between retinal neurodegeneration and microvascular complications of retinopathy are still unclear [13] Numerous possible mechanisms have been demonstrated including chronic hyperglycemia induced low grade inflammation, oxidative stress, and ischemia of neurovascular structures, which finally lead to neural apoptosis, glial cell reactivity, extracellular glutamate accumulation and Muller cell activation, are thought to be associated with both retinal neurodegeneration and microvascular manifestations of diabetes [13, 14].

Recent advances in OCT device technologies allow early visualization of retinal neurovascular impairments before any sign of clinically detectable retinopathy. Several clinical studies showed the retinal neurodegeneration in diabetic patients with or even without clinically appearant retinopathy. Pierro et al. reported that type 2 diabetic patients with early stage retinopathy and without retinopathy have inferior thickness values of ganglion cell complex [15]. Zhu et al. studied the changes in retinal thickness and visual function (contrast sensitivity and pattern ERG) in type 2 diabetic patients without clinical evidence of DR. The results indicated that ganglion cell complex thickness and visual function changes could be observed in diabetic subjects before the onset of any significant DR. Macular ganglion cell complex reduction occurred much earlier than peripapillary retinal nerve fiber layer thinning in diabetic patients without retinopathy [4]. Toprak et al. investigated retinal layer reflectivities in patients with mild non-proliferative diabetic retinopathy and showed the impaired inner segment elipsoid layer reflectivity, which might indicate the photoreceptor degeneration [16]. Ng *et al.* reported a thinning of both RNFL and ganglion cell+inner plexiform layers in diabetic eyes with no signs of retinopathy [17]. van Dijk et al. studied the inner layer thickness of type 1 diabetes patients and concluded that thinning of the total retina in type 1 diabetic patients with minimal retinopathy compared with healthy controls is attributed to a selective thinning of inner retinal layers and supports the concept that early DR includes a neurodegenerative component [6].

Insulin has multiple effects in neurons including the regulation of neuronal proliferation, apoptosis, synaptic transmission and neuronal degeneration [18]. Insulin is suggested to have neuroprotective properties and to exert neurotrophic effects on neurons [19]. Metabolic changes resulting from IR can impact on the neuronal structure, resulting in synaptic dysfunction and promoting triggers of neurodegeneration such as impaired neuronal insulin signalling, vascular endothelial damage, neuroinflammation, tau phosphorylation and amyloid β accumulation [19]. Arıkan et al. reported that the mean average ganglion cell-inner plexiform layer thickness in insulin resistant patients was significantly less in comparison with the healthy subjects. In the same study, there were no statistically significant differences between the two groups in any of the spatial frequencies in the functional acuity contrast test [12]. Similarly, in the present study, it was found that the average, the inferior, and the temporal quadrant RNFL thicknesses in subjects with IR were significantly less than those of the control group and our results indicate IR has an early neurodegenerative effect on the retina.

Although the molecular mechanism by which neurons die under oxidative stress induced by high glucose remains largely unclear, hyperglycemia was believed as the most important factor in neurodegeneration seen in diabetic patients [20]. Additional pathophysiologic mechanism should be present in individuals with IR since plasma glucose levels remain within normal limits. IR, in which a higher insulin concentration is required to maintain glucose uptake into cells via insulin-dependent glucose transporters, has been implicated to have a role in the pathophysiologic mechanisms of neurodegenerative diseases such as Alzheimer's disease [21]. Functional insulin

signaling pathway is crucial for neuronal cell survival. Karaca *et al.* reported that the patients with metabolic syndrome have inner and outer retinal thinning on OCT segmentation analysis. They investigated the retinal neurodegenerative factors in patients with metabolic syndrome other than hyperglycemia and speculated that IR, low grade sytemic inflammation and hypertension-related endothelial damage might have a neurodegenerative effect independent of the hyperglycemia [11].

Our study may have some limitations. The disease duration and severity may have an effect on retinal nerve fiber layer thickness layer measurements and analysis of these patients based on disease duration might have provided more clear data. Our study population was relatively small, although significant RNFL changes were measured in several quadrants.

In the current study, we investigated the impact of insulin resistance on retinal neural structure. In conclusion, our results provided the proof that early neurodegeneration existed in the retina of prediabetic patients with IR.

Conflict of Interest: The authors declare no conflict of interests.

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