·Clinical Research·

Retinal nerve fiber layer and ganglion cell-inner plexiform layer thickness in children with obesity

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Abstract

• **AIM: To evaluate retinal nerve fiber layer (RNFL) thickness analysis of peripapillary optic nerve head (PONH) and macula as well as ganglion cell-inner plexiform layer (GCIPL) thickness in obese children.**

• **METHODS: Eighty-five children with obesity and 30 controls were included in the study. The thicknesses of the PONH and macula of each subject's right eye were measured by high-resolution spectral-domain optic coherence tomography (OCT).**

• **RESULTS: The RNFL thicknesses of central macular and PONH were similar between the groups (all P >0.05). The GCIPL thickness was also similar between the groups. However, the RNFL thickness of temporal outer macula were 261.7 ±13.7 and 268.9 ±14.3 μm for the obesity and the control group, respectively (P =0.034).**

• **CONCLUSION: Obesity may cause a reduction in temporal outer macular RNFL thickness.**

• **KEYWORDS:** ganglion cell-inner plexiform layer; retinal nerve fiber layer thickness; optical coherence tomography; obesity

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INTRODUCTION

Obesity, one of today's leading health concerns in the community, is a low-grade chronic inflammatory disease. The disease is closely associated with life-threatening diseases such as hypertension, diabetes mellitus, stroke, metabolic syndrome, *etc*. The most possible mechanism involved in the development of obesity-related co-morbidities is the imbalance between the reactive oxygen radicals generation and the antioxidant activity in cells, generally called "oxidative stress" [1]. Obesity-related cardiometabolic disorders are known to be associated with visual impairment as well [2-3]. For instance, increased body mass index (BMI) was associated with early age-related macular degeneration in female non-smokers [4]. Moreover, it is well known that diabetes mellitus, closely related to obesity, is one of the leading causes of blindness. Further, obesity may lead increased intraocular pressure and glaucoma [3,5-6]. Retrobulbar adipose tissue volume may be an effect upon intraocular pressure in obesity[7].

Outside of concomitant diseases, obesity itself directly impairs the function of many organ systems *via* obesity-related oxidative stress and lipotoxicity [8]. The disease is associated with low grade chronic inflammation, a common feature of many complications of obesity that appears to emanate in part from adipose tissue. In obese rodents adipose tissue macrophage accumulation is a critical component in the development of obesity-induced inflammation [9-10]. It was recently described that a novel macrophage cell death pathway that occurs when toll-like receptor 4 is activated under lipotoxic conditions[11]. The mechanism of this response involves the intersection between mediators which are modulating toll-like receptor signaling pathways and impaired lysosome function and integrity. High fat diet-induced obesity is accompanied by increased hepatic, heart, and renal tissues oxidative stress, which is characterized by reduction in the antioxidant enzymes activities and glutathione levels, that correlate with the increase in some oxidant factors levels including malondialdehyde and protein carbonyl in most tissues[12].

Optical coherence tomography (OCT), which uses near infrared light to provide cross-sectional images of the retinal architecture, enables physicians to noninvasively and objectively quantify the measurement of retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thickness[13]. Recent advances in OCT technology have enabled an automatic segmentation between the RNFL and GCL in the macula[14].

Retinal ganglion cells (RGCs) are particularly vulnerable to metabolic and oxidative damage in the eye [15]. To the best of our knowledge, there are no studies in the literature evaluating these macular thickness parameters as well as

macular GCL in obese children by OCT. The goal of this study is to evaluate RNFL and RGC thickness and reveal to their association with obesity in pediatric population.

SUBJECTS AND METHODS

Subjects The pediatric subjects were recruited at the Gaziosmanpaşa University Hospital (Tokat, Turkey) for this observational cross-sectional study. This study was approved by the Ethics committee of the Gaziosmanpaşa University, which adhered to the tenets of the Declaration of Helsinki. Participation in the study was voluntary and written informed consent for participation in the study was obtained from the parents or guardians as well as the participants.

Consecutive eighty-five obese children who attending pediatric obesity clinic in our hospital age 7 to 15y were included in this study and 30 age-sex-matched non-obese children who attending eye clinic of our hospital with non-specific ocular complaints, such as conjunctivitis, burning, itching, or refractive errors were selected randomly as a control group.

Determination of the Groups and Calculation of the Body Mass Index Height was measured without socks and shoes using a calibrated vertical portable stadiometer, to the nearest millimeter. Weight was measured with light clothing using a digital electronic weighing scale, to the nearest decimal fraction of a kilogram. BMI was calculated as weight in kilograms divided by the square of height in meters. Then, BMI for age categories and corresponding percentiles are: 1) healthy weight: the 5th percentile to less than 85th percentile included in the control group; 2) equal to or greater than 95th percentile included in the obesity group.

The Eye Examination and the Procedure of Optical Coherence Tomography Measurements Each participant underwent an ophthalmologic evaluation that included best-corrected visual acuity measurement, slit-lamp evaluation, indirect ophthalmoscopy, intraocular pressure measurement, and spectral-domain optic coherence tomography (SD-OCT) scanning.

OCT scanning was performed only for right eyes of each participant using the Cirrus high-resolution SD-OCT system (Carl Zeiss Meditec, Dublin, CA, USA). Scans were performed by one trained technician. An internal fixation target was used to improve reproducibility, and a patch was placed over the left eye. Scans were performed without flash photography to optimize patient comfort. Pupils were dilated with 1% tropicamide before at least 30min to measurements. Good quality scans were defined according to specifications in the user manual; criteria included signal strength $\geqslant$7 (maximum 10), centering of the scan, and uniform brightness. Measurements were repeated until obtaining sufficient quality.

Third OCT scanning protocols were performed on the right eye. First, the optic nerve head (ONH) cube protocol computes the RNFL thickness along 2.4-mm diameter circles around the optic disc. In the ONH cube measurements, the following software-provided parameters were evaluated: average RNFL thickness in the 4 quadrants, and global average RNFL thickness and optic disc diameter size. Second, the macular cube 512×128 scanning protocol was used to image a 6×6×2-mm^3 cube of macular tissue centered on the fovea. The macular cube protocol consists of 128 horizontally oriented B-scans, each 6 mm in length and composed of 512 equally spaced transverse sampled locations. All 128 OCT B-scans are acquired in a continuous, automated sequence and cover a 6×6-mm^2 area. This scan protocol provides a pixel by pixel significance map and nine parameters from a circular grid based on the Early Treatment Diabetic Retinopathy Study. The map is composed of sectoral thickness measurements in three concentric circles with diameters of 1, 3 and 6 mm. Each ring is divided into superior, nasal, inferior and temporal quadrants. The retinal thickness of each of the nine subfields of the Early Treatment Diabetic Retinopathy Study like map was recorded. Third, ganglion cell-inner plexiform layer (GCIPL) scanning protocol [16]. Briefly, the ganglion cell analysis algorithm identifies the outer boundary of the RNFL and the outer boundary of the inner plexiform layer, which contains the retinal ganglion cell dendrites. In the image data, the boundary between these two layers is anatomically indistinct so that they are difficult to distinguish from each other, but the combined thickness is considered to be indicative of the health of RGCs. The average and sectoral (superotemporal, superior, superonasal, inferonasal, inferior, inferotemporal) thicknesses of the GCIPL are measured in an elliptical annulus (dimensions: vertical inner and outer radius of 0.5 mm and 2.0 mm, horizontal inner and outer radius of 0.6 and 2.4 mm, respectively) around the fovea[16].

RESULTS

A total of 115 subjects (115 eyes) were examined with the SD-OCT: 85 eyes with obese children and 30 eyes with non-obese children. The mean ages were 10.8±2.9 (6-15) and 11.1±2.8 (6-16) years old, for the obesity and the normal group, respectively. The male/female ratio was 42/43 in the obese group and 16/14 in the normal group (P>0.05 for age and gender). The spherical refraction and intraocular pressure values of patients were similar in both groups (P>0.05). The demographic characteristics of patients are presented in Table 1.

Table 2 shows macular thickness measurements estimates in right eyes of the two groups. Average RNFL thickness of temporal outer macula (TOM) were 261.7±13.7 μm and 268.9±14.3 μm for the obesity and the normal group, respectively(P=0.034). There were no significant differences in the other macular thickness measurements of the subfield

Table 1 Demographic characteristics of children with obesity and control subjects $\bar{x} \pm s$

Parameters	Obesity (n=85)	Control (n=30)	P
Age (a)	10.8±2.9	11.1±2.8	0.623
Gender, n(%)			0.713
M	42	16	
F	43	14	
Spherical refraction	-0.40±0.65	-0.25±0.57	0.194
Intraocular pressure[a] (mm Hg)	14.22±3.27	13.15±2.5	0.421

[a]Goldmann applanation tonometer value of intraocular pressure adjusted for central corneal thickness.

Table 2 Average RNFL thicknesses measurements of the subfield areas of the Early Treatment Diabetic Retinopathy Study-like map of macula in obese and non-obese children $\bar{x} \pm s$

Parameters (μm)	Obesity (n=85)	Control (n=30)	P
CSF	245.3±20.6	239.3±18.8	0.197
SIM	319.9±16.7	318.2±13.7	0.625
NIM	320.6±17.1	319.2±16.1	0.719
IIM	317.3±15.7	318.7±13.2	0.669
TIM	307.1±13.9	311.7±26.4	0.266
SOM	280.5±14.4	286.9±18.6	0.087
NOM	298.1±17.9	300.3±17.1	0.601
IOM	272.1±19.4	277.1±11.1	0.121
TOM	261.7±13.7	268.9±14.3	0.034

CSF: Central subfield; SIM: Superior inner macula; NIM: Nasal inner macula; IIM: Inferior inner macula; TIM: Temporal inner macula; SOM: Superior outer macula; NOM: Nasal outer macula; IOM: Inferior outer macula; TOM: Temporal outer macula.

areas of the Early Treatment Diabetic Retinopathy Study-like map between the two groups (P>0.05).

The average GCIPL thickness were 84.9±5.2 μm and 84.9±5.7 μm in the groups of obesity and control, retrospectively (P =0.976). There was also no difference in other subfield GCIPL thickness between the studied groups (P > 0.05). The GCIPL subfield parameters are presented in Table 3.

The average optic disc size were 1.98±0.35 μm and 1.97±0.37 μm and the average peripapillary RNFL thickness were 97.45±10.28 μm and 97.49±9.06 μm in the groups of obesity and control, respectively (P>0.05 in both parameters). Table 4 shows the other subfield peripapillary RNFL thickness between the studied groups and there was also no significant difference (P > 0.05).

DISCUSSION

Obesity, low-grade chronic inflammatory disease, affects almost all organs. It has been hypothesized that the state of chronic low-grade inflammation associated with excess adipose tissue may explain the development of the obesity-related pathologies, such as type 2 diabetes mellitus and cardiovascular disease [17-18]. Suppressors of cytokine signaling caused by chronic inflammation or cellular stress can induce insulin resistance and inhibit neurotrophic factors, such as ciliary neurotrophic factor, leukemia inhibitory factor, and insulin, that are essential for retinal cell survival [19]. Moreover, it is argued that obesity in children may cause

Table 3 Average ganglion cell-inner plexiform layer thickness in obese and non-obese children $\bar{x} \pm s$

Parameters (μm)	Obesity (n=85)	Control (n=30)	P
Average thickness	84.9±5.2	84.9±5.7	0.976
Nasal superior	85.6±6.1	85.5±8.3	0.937
Nasal inferior	85.9±5.9	85.6±7.3	0.887
Inferior	84.9±5.8	84.7±6.4	0.847
Temporal inferior	84.3±5.7	84.9±6.1	0.642
Temporal superior	84.9±5.9	84.8±6.6	0.921

Table 4 Mean peripapillary retinal nerve fiber layer thickness in eyes of children with obesity and control subjects $\bar{x} \pm s$

Parameters (μm)	Obesity (n=85)	Control (n=30)	P
Optic disc size	1.98±0.35	1.97±0.37	0.907
Superior quadrant	123.64±15.07	125.90±13.39	0.540
Nasal quadrant	70.51±10.26	73.00±12.95	0.356
Inferior quadrant	127.53±18.84	124.05±17.75	0.465
Temporal quadrant	68.13±10.84	67.00±8.57	0.664
Average thickness	97.45±10.28	97.49±9.06	0.504

increased intraocular pressure, which may affect the RNFL thickness [6]. It is shown in the a recent study that elevated intraocular pressure may be caused by changes in ocular blood flow, affected by the physical pressure exerted by higher retrobulbar adiposity, and/or by internal vascular changes secondary to complications of obesity [7]. Therefore, the present study was designed to examine for the first time in the literature whether RNFL thicknesses of macular and peripapillary optic nerve head (PONH) as well as GCIPL thickness in children with obesity differed from those of age- and sex-matched healthy controls. We found that, in this study, RNFL thickness of TOM was decreased in children with obesity. However, the GCIPL thickness of children with obesity was similar with control subjects.

The obese children might have elevated levels of oxidative stress products, which may contribute to long-term complications [20]. It is postulated that obesity related low-grade inflammation can cause neurological diseases such as Parkinson's and Alzheimer's [21-22]. Neuronal membranes are rich in polyunsaturated fatty acids (PUFAs), particularly arachidonic acid, decosahexaenoic acid, and eicosapentaenoic acid [23]. The neural cells are more susceptible to oxidative damage due to their possession of unsaturated double bounds[24]. In spontaneous obese rat model, Reddy *et al* [25] have documented that altered ubiquitin-proteasome system one of the underlying mechanisms for the neuronal cell death. This system is essential in regulating a host of cell signaling pathways involved in proliferation, adaptation to stress, regulation of cell size, and cell death [26]. These cellular changes induced by obesity are also observed in retinal cells. Mancini *et al* [27] showed in diabetic neonatal rats fed on a high-fat-diet that there is a significantly higher frequency of vessel abnormalities in the form of acellular capillaries and

loss of pericytes as well as ganglion cells. Besides its well-known effects on the retinal cells through its oxidative stress products, obesity also has an effect on visual system *via* its effect on central nervous system[28].

Increased intraocular pressure can lead to visual loss *via* death of ganglion cells. There are many studies claimed that obesity can cause IOP elevation and glaucoma[3,6-7,29]. In obese people, elevated intraocular pressure may be caused by changes in ocular blood flow, affected by the physical pressure exerted by higher retrobulbar adiposity, and/or by internal vascular changes secondary to complications of obesity [7]. In a cross-sectional and longitudinal study, it is suggested that blood pressure and BMI are positively associated with IOP in middle-aged and older Japanese[5]. In a study of Akinci *et al* [6] performed on obese children, it is documented that obesity is also an independent risk factor for increased IOP besides to its indirect effect on IOP *via* blood pressure change. The choroidal blood flow is important for the health of the retinal cell besides the increase in intraocular pressure. Decreased ocular blood flow and choroidal perfusion may also be an effect on retinal cells in the obese individuals [30]. Although many of studies have shown that obesity is associated with increased IOP, some studies have failed to show this relationship[31-32].

The ability to maintain adequate nutrient supply to retina such as ganglion cells, despite variations in metabolic demand, the driving pressure for blood flow, or the oxygen or carbon dioxide content of blood, is critical to maintenance of normal function [33]. Therefore, conditions such as obesity which lead to changes in ocular blood flow may have a detrimental effect on retinal cells. Li *et al* [34] found that higher BMI was associated with narrower retinal arteriolar, wider venular caliber, and increased retinal venular tortuosity. In an experimental study [35], retinal blood flow reduction was noticed in obese mice. Moreover, retinal thickness of the nerve fiber layer to inner plexiform layer was also significantly reduced in obese mice compared to that in wild-type mice. However, no obvious differences in capillary vessel densities of the intermediate and deep capillary layers were detected between normal and obese mice in that study.

Measurement of the RNFL thickness by OCT, provides additional useful information in the diagnosis and management of retinal pathologies including some of inflammatory illnesses in children[36]. However, measurement of the RNFL thickness of retina by OCT is affected by both refractive status and age of children[37-38]. We have eliminated these potential confusing factors by using age and sex matched controls and it was demonstrated that the 2 groups had statistically similar refractive errors.

The study was limited by the small sample size and the lack of statistical significance on essentially most of the investigated comparisons except for the TOM thickness. Further research, including large-case series, is needed to clarify whether obesity have an effect on GCL thickness.

In conclusion, it was found in this study that RNFL thickness of TOM was decreased in children with obesity. However, RNFL thickness of outer macular subfield areas did not differ. The RNFL thicknesses of PONH and GCIPL were not significantly different in children with obesity from those of controls.

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