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Evaluation of Ganglion Cell-Inner Plexiform and Retinal Nerve Fiber Layer Thicknesses in Obese Children and Their Associations with Obesity Severity and Duration

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ABSTRACT

Aim: To evaluate the macular ganglion cell-inner plexiform layer (GC-IPL) and the retinal nerve fiber layer (RNFL) thicknesses measured by high-definition optical coherence tomography (HD-OCT) in children with obesity and to determine whether thickness parameters are correlated to disease severity and duration.

Materials and Methods: This prospective study involved 40 obese and 40 age and sex-matched non-obese children aged between 6 and 17 years. Following the measurement of body mass index (BMI), cycloplegic auto-refraction, intraocular pressure, and axial length (AL) was measured. OCT scans were performed using Cirrus HD-OCT (Carl-Zeiss Meditec, Dublin, CA, USA). Right eye of each subject was selected for analysis.

Results: The study included 40 healthy children and 40 children with obesity. The RNFL thickness measurements revealed thinner in the obesity group compared to controls for all quadrants however, the only statistically difference were for the average and superior quadrants ($P < 0.05$). All GC-IPL thickness parameters were statistically thinner in the obese subjects compared to the controls ($P < 0.05$). Average peripapillary RNFL and macular GC-IPL thicknesses and some quadrants and sectors are inversely correlated with disease severity and duration.

Conclusions: Macular GC-IPL and peripapillary RNFL thicknesses were significantly lower in obese children than controls and a negative correlation between the severity and duration of obesity and both the GC-IPL and RNFL thicknesses could indicate that obesity control in children may be a crucial strategy for prevention of glaucoma.

Key Words: *GC-IPL and RNFL thicknesses, Obese children*

Obez Çocuklarda Ganglion Hücre İç Pleksiform ve Retina Sinir Lifi Tabakası Kalınlıklarının ve Obezite Şiddeti ve Süresi ile Birlikteliğinin Değerlendirilmesi

ÖZ

Amaç: Obez çocuklarda maküler gangliyon hücre iç pleksiform tabakası (GH-IPT) ve retina sinir lifi tabakası (RSLT) kalınlıklarının yüksek çözünürlüklü optik koherens tomografi (OKT) ile değerlendirilmesi ve kalınlık parametrelerinin hastalık şiddeti ve süresi ile korele olup olmadığını belirlemek.

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Gereç ve Yöntemler: Bu prospektif çalışmaya, 6 ve 17 yaşları arasında 40 obez çocuk ve 40 obez olmayan eşit yaş ve cinsiyette sağlıklı çocuk dahil edildi. Vücut kitle indeksi (VKI) ölçümünü takiben, sikloplejik oto-refraksiyon, göz içi basıncı (GİB) ve aksiyel uzunluk (AU) ölçüldü. OKT taramaları Cirrus HD-OCT (Carl-Zeiss Meditec, Dublin, CA, ABD) kullanılarak yapıldı. Analiz için her bireyin sağ gözü seçilmiştir.

Bulgular: Çalışmaya 40 sağlıklı çocuk ve 40 obez çocuk alındı. RSLT kalınlığı ölçümleri obezite grubunda tüm kadranlar için kontrollere kıyasla daha ince bulundu, ancak istatistiksel olarak tek fark ortalama ve üst kadranlar için idi (P <0.05). Tüm GH-IPT kalınlık parametreleri obez olgularda kontrollere göre istatistiksel olarak daha düşüktü (P <0.05). Ortalama peripapiller RSLT kalınlığı ve maküla GH-IPT kalınlığı, bazı kadranlar ve sektörler hastalık şiddeti ve süresi ile ters orantılıdır.

Sonuç: Maküler GH-IPT ve peripapiller RSLT kalınlıkları obez çocuklarda kontrollere göre anlamlı olarak düşüktü. Hem GH-IPT hem de RSLT kalınlıkları ile obezitenin şiddeti ve süresi arasında negatif bir korelasyon vardı. Çocuklarda glokomun önlenmesi için obezite kontrolünün çok önemli bir strateji olabileceğini düşündürdü.

Anahtar Sözcükler: *GH-IPT ve RSLT kalınlıkları, Obez çocuklar*

INTRODUCTION

Childhood obesity has become a major public health problem (1). The World Health Organization described it as a growing global epidemic closed to 10% of children worldwide (2). The impact of childhood obesity on health is on a large scale (3,4). In obese children, an increased risk has been shown for several diseases including precocious puberty, gynecomastia, polycystic ovary syndrome, diabetes mellitus type 2, and hypertension (5-8). Besides this, childhood obesity has been associated with increased adult risk of coronary heart disease, diabetes mellitus, colorectal cancer, and premature death (8,9).

The glaucoma is a progressive optic neuropathy that can result in irreversible blindness. Progressive damage continues despite intraocular pressure (IOP) reduction with treatment in some patients with glaucoma (10). Besides the increased IOP, there are several other factors associated with glaucoma progression such as neurotoxicity, reduced ocular blood flow (11-13), ocular vascular dysregulation (14) and changes in systemic blood pressure (15,16). Some studies found that obesity is a risk factor for increased IOP (17,19,30), as well as systemic vascular abnormalities such as hypertension and arteriosclerosis (2). On the contrary, there are few studies on obesity and no connection with IOP (31,32,33). Therefore, relationship between obesity and IOP has not been clarified.

Body mass index (BMI) is one of the most specific and objective measurement to define obesity. Obesity in children is defined as a BMI *z*-scores, also called BMI standard deviation scores, are measures of relative weight adjusted for child age and sex (20, 21). Although several studies have evaluated the effect of obesity on IOP (19, 20, 21), there are limited previous studies evaluating the association of BMI with optical coherence tomography (OCT) findings in obese children and no studies have evaluated the ganglion cell-inner plexiform layer (GC-IPL) thickness.

Hence, the purpose of this study is to investigate and compare thicknesses of macular GC-IPL and peripapillary retinal nerve fiber layer (RNFL) in different sectors using Cirrus high definition OCT (HD-OCT) in obese children with age and sex-matched controls. In addition, we assessed whether thickness parameters are correlated with obesity severity and duration.

MATERIALS and METHODS

The prospective study was conducted in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and approved by the Local Ethics Committee of the participating center. Written informed consent was obtained from the parents of the children after explaining the imaging modality to them and to the child.

Forty obese children were recruited randomly from the Department of Pediatric Endocrinology. The control group consisted of 40 non-obese age and sex-matched children, who were recruited among the school children. Measurements from the right eye were used for statistical analysis. All children were included in this study had best corrected visual acuity (BCVA) of -0.10 to 0.10 logMAR. Exclusion criteria included low OCT signals, high refractive error (in spherical equivalent) exceeding ± 3.0 diopters (D) and astigmatism exceeding 2.0 D, and ocular conditions, such as strabismus, amblyopia or any retinal or optic disc anomaly including tilted disc and the presence of cardiovascular, renal, neurological, mental or metabolic disorders and genetic syndromes.

Height and weight measurements were performed first. Weight and height were measured with the children wearing light clothes and no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Various classification schemes are currently used to define the overweight and obese adults however, no scheme is present to define overweight and obese children or adolescents. In this study we defined the obesity using the BMI z-scores. A child with a BMI in the 95th percentile or greater was considered to be obese and a child with a BMI lower than 95th percentile was considered as normal (22, 23). Obesity duration information of all obese children obtained from the Department of Pediatric Endocrinology and recorded.

Each subject underwent an initial ophthalmic examination including measurement of the cycloplegic refraction, IOP, and axial length (AL). IOP was examined by Tono-Pen (Reichert Tono-Pen AVIA) three times. Pupillary dilation was induced by three cycles of cyclopentolate 1% (1 drop), administered 5 minutes apart. Thirty to 40 minutes after administration of the eye drops, the autorefractometer (Topcon KR 8800, Japan) was set to generate three valid readings of refraction, and the median value given by the instrument was used for analysis. Spherical equivalent (SE) refraction was calculated as the sum of the value of the spherical value and half of the cylindrical value. AL was determined by the Nidek AL-Scan optical biometer (Nidek CO, LTD.)

After pupillary dilation, OCT scans were performed using Cirrus HD-OCT (Carl-Zeiss Meditec, Dublin, CA, USA). The Cirrus HD-OCT provides 27,000 A-scans with a depth resolution of 5 μm and a transverse resolution of 20 μm using an 840-nm super luminescence diode. A 512 × 128 macular cube scan and a 200 × 200 optic disc cube scan were performed on each eye. On the basis of the obtained OCT image, the following parameters were measured automatically: GC-IPL thickness, RNFL thickness, central foveal thickness (CFT), disc area, rim area, horizontal and vertical cup-to-disc ratio (CDR). The optic nerve head (ONH) measurements were consisted of rim area (mm^2), disc area (mm^2), and average and vertical CDR. The prototype ganglion cell analyzes (GCA) algorithm, incorporated in Cirrus HD-OCT software Version 6, was used to measure the GC-IPL thickness within a 14.13 mm^2 elliptical annulus area centered on the fovea. A signal strength ≥ 6 was considered acceptable. Internal fixation targets were used for proper alignment of the eye, and all imaging work was performed by an experienced operator. The patients were requested to sit, place the chin on the chin rest, and lean their forehead against the headrest of the device, upright with the eye focusing on an internal fixation target without blinking and eye movement while six radial retinal scans were performed.

The right eye from each patient was selected and used for analysis. Statistical analysis was performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Normality of all data samples was checked by means of the Kolmogorov–Smirnov test. The measurement differences between the obese and non-obese children were evaluated by the independent two-sample t-test. Pearson's correlation coefficients were calculated to assess the correlation between HD-OCT measurements (GC-IPL and RNFL thickness) and obesity severity and duration. P value less than 0.05 was considered to be statistically significant.

RESULTS

Forty obese children (22 boys, 18 girls), aged 6 to 17 years were included in the study group. All had a BMI ≥ 25 kg/m^2 (range 25.2 to 38.8 kg/m^2). Obesity duration ranged from 1 to 7.5 years with a mean of 3.35 ± 1.23 years. There were 40 age and sex-matched controls. BMI of controls ranged between 17.5 and 24.2 kg/m^2. There was no statistically difference between the obese and control subjects in terms of SE and AL. However, the mean IOP was significantly higher in the obese group ($P = 0.030$) (Table 1).

The mean RNFL thickness were 91.08 ± 6.02 μm in patients with obesity and 94.85 ± 7.12 μm in controls, respectively. ($P = 0.012$). The RNFL thickness measurements revealed thinner in the obesity group compared to controls for all quadrants however, the only statistically difference was for the superior quadrant ($P = 0.002$).

There was no statistically difference between the obese and control subjects in terms of disc area and rim area. However, the average and vertical CDR were significantly larger in the obese group ($P = 0.012$ and 0.015 respectively) (Table 2).

Average, minimum, and six-sectorial GC-IPL thicknesses were also analyzed in this study. All GC-IPL thickness parameters were statistically thinner in the obese subjects compared to the controls ($P < 0.05$) (Table 3).

Correlation analyses are shown in Table 4. Obesity severity was inversely correlated with average and temporal RNFL thicknesses (P were 0.034 and 0.048, respectively). Average ($P = 0.008$), superonasal ($P = 0.033$), inferior ($P = 0.004$), inferotemporal ($P = 0.036$), and inferonasal ($P = 0.002$) GC-IPL thicknesses were also inversely correlated with obesity severity. Obesity duration was inversely correlated with average and superior RNFL thicknesses (P were 0.042 and 0.002, respectively). Average ($P = 0.001$), minimum ($P = 0.032$), superior ($P < 0.001$), superonasal ($P < 0.001$), inferior ($P = 0.003$), and inferonasal ($P < 0.001$) GC-IPL thicknesses were also inversely correlated with the obesity duration.

DISCUSSION

The inner layer of the retina, including the GCL, IPL and RNFL has been recently scanned and evaluated with HD-OCT (26). Ganglion cells are multilayered and have the highest concentration within the macula. Diagnostic ability of the GCL measurement is superior to the RNFL thickness measurement in early glaucoma and is comparable in moderate and advanced glaucoma (27, 28).

Obesity has been shown to cause vascular endothelial and autonomic dysfunction (24, 25). Some authors argue that obesity increases IOP due to an excessive intraorbital

Table 1: Demographics of patients with obese and non-obese children

	Obese Children	Non-obese Children	P value
Age (years)	11.73 ± 2.85	11.73 ± 2.85	1.00
BMI (kg/m²)	29.18 ± 3.55	21.12 ± 1.75	< 0.001
Obesity duration (years)	3.35 ± 1.23	---	---
IOP (mm Hg)	16.01 ± 1.81	14.82 ± 1.43	0.030
Spherical equivalent (D)	-0.19 ± 0.48	-0.05 ± 0.70	0.30
Axial Length (mm)	23.37 ± 0.82	23.41 ± 0.82	0.80

BMI: Body mass index, **IOP:** Intraocular pressure, **D:** Diopter.
P < 0.05 indicates statistically significance (independent two-sample t-test).

Table 2: Comparison of RNFL thickness and ONH parameters among obese and non-obese children

	Obese Children	Non-obese Children	P value
RNFL Thickness (µm)			
Average	91.08 ± 6.02	94.85 ± 7.12	0.012
Superior	111.75 ± 12.89	120.90 ± 12.40	0.002
Inferior	120.50 ± 10.73	123.80 ± 13.52	0.230
Nasal	66.25 ± 7.60	67.85 ± 7.43	0.344
Temporal	65.75 ± 9.05	66.35 ± 8.03	0.755
ONH parameters			
Rim area (mm²)	1.48 ± 0.23	1.52 ± 0.19	0.430
Disc area (mm²)	1.86 ± 0.29	1.81 ± 0.33	0.443
Average C/D ratio	0.42 ± 0.13	0.34 ± 0.17	0.012
Vertical C/D ratio	0.40 ± 0.13	0.32 ± 0.17	0.015

C/D: Cup-to-disc, **RNFL :** Retinal nerve fiber layer, **ONH:** Optic nerve head.
P < 0.05 indicates statistically significance (independent two-sample t-test).

Table 3: Comparison of GC-IPL thickness among obese and non-obese children

	Obese Children	Non-obese Children	P value
GC-IPL Thickness (µm)			
Average	81.08 ± 3.96	84.55 ± 3.84	< 0.001
Minimum	78.38 ± 3.83	81.35 ± 4.66	0.003
Superior	80.98 ± 4.25	85.47 ± 3.54	< 0.001
Superonasal	81.13 ± 4.20	85.32 ± 4.76	< 0.001
Superotemporal	80.93 ± 4.39	83.82 ± 4.10	0.003
Inferior	80.65 ± 5.06	83.95 ± 4.13	0.002
Inferonasal	81.10 ± 5.31	84.60 ± 4.97	0.003
Inferotemporal	81.33 ± 4.37	84.35 ± 3.90	0.002

GC-IPL: Ganglion cell–inner plexiform layer.
P < 0.05 indicates statistically significance (independent two-sample t-test).

Table 4: Correlation of RNFL and GC-IPL thicknesses with the severity and duration of obesity

	Obesity severity		Obesity duration	
	Correlation Coefficient	P value	Correlation Coefficient	P value
RNFL Thickness (µm)				
Average	-0.336	0.034	-0.322	0.042
Superior	-0.232	0.150	-0.484	0.002
Inferior	-0.276	0.085	-0.164	0.311
Nasal	-0.208	0.165	0.057	0.726
Temporal	-0.316	0.048	-0.042	0.795
GC-IPL Thickness (µm)				
Average	-0.415	0.008	-0.524	0.001
Minimum	-0.286	0.074	-0.339	0.032
Superior	-0.271	0.090	-0.530	< 0.001
Superonasal	-0.338	0.033	-0.557	< 0.001
Superotemporal	-0.151	0.352	-0.295	0.065
Inferior	-0.445	0.004	-0.453	0.003
Inferonasal	-0.485	0.002	-0.546	< 0.001
Inferotemporal	-0.333	0.036	-0.278	0.083

GC-IPL: Ganglion cell–inner plexiform layer, **RNFL:** Retinal nerve fiber layer. P < 0.05 indicates statistically significance (Pearson correlation).

adipose tissue deposit, leading to a rise in blood viscosity and episcleral venous pressure, and a consequent decrease in the facility of aqueous outflow. On the other hand, there's too much studies not to be ignored, reporting that no relationship between obesity and IOP and glaucoma progression (31,32,33). Consequently, this topic is not clear.

Kocak et al evaluated the IOP values of children with normal and high BMI and to obtain the potential correlation between glaucoma and obesity. there were no significant difference in IOP values, cup/disc ratios and visual field defects between obese and healthy children. No significant correlation was found between obesity and glaucoma or elevated IOP in children (31).

Some studies have reported a relationship between obesity and IOP in both adults and children (19,20,21,30). Cohen et al evaluated the prospect of a relationship between BMI and IOP in both men and women. Cohen et al reported that obesity is an independent risk factor for increasing IOP in both men and women (30). Although authors focus IOP and blood flow parameters on obesity, there are limited previous studies evaluating the association of childhood obesity and RNFL thickness and no study has evaluated the GC-IPL thickness. According to our literature knowledge, this prospective study is the first to evaluate the measurements of the peripapillary RNFL, and GC-IPL in obese children as well as the association of those parameters with the severity and duration of obesity.

Pacheco-Cervera et al reported that adiposity and obesity-related inflammatory factors may be associated with the loss of RNFL in children (29). RNFL thicknesses on the average, inferior, superior, and nasal quadrants were decreased in severely obese children. Besides, there was a significant inverse correlation of RNFL thickness with adiposity indices. In accordance with previous study, we showed that the average and four quadrants of RNFL thicknesses were lower in obese children. Average and nasal RNFL thicknesses were significantly lower in obese children compared with non-obese children, whereas the other sectorial thicknesses did not show any significant difference. In addition, there was a significant inverse correlation of average and temporal thicknesses with obesity severity, and average and superior quadrant thicknesses with obesity duration.

In our study the mean IOP was significantly higher in the obese group. Average, minimum, and six-sectorial thicknesses and all GC-IPL thicknesses were statistically significantly lower in obese children when compared with controls. In contrast to the peripapillary RNFL thickness measurements, GC-IPL thickness is reduced globally in obese children without any specific sectorial preference. Besides, average, superonasal, inferior, and inferonasal GC-IPL thicknesses were inversely correlated with both obesity severity and duration. However, inferotemporal sector was inversely correlated with only obesity severity and minimum and superior sectors were inversely correlated with only obesity duration. As obesity tends to continue into adulthood, a negative correlation between the severity and duration of obesity and both the RNFL and GC-IPL thicknesses could indicate that obesity control in children is a crucial strategy for prevention of glaucoma.

In conclusion, we observed that the peripapillary RNFL and macular GC-IPL thicknesses were significantly lower in obese children than controls. Furthermore, average peripapillary RNFL and macular GC-IPL thicknesses as well as some quadrants and sectors are inversely correlated with disease severity and duration. However, further studies with larger population and long follow-up time should be performed to explore and conceive the effect of childhood obesity on glaucoma development.

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