European Review for Medical and Pharmacological Sciences 2016; 20: 886-891

The retinal nerve fiber layer, choroidal thickness, and central macular thickness in morbid obesity: an evaluation using spectral-domain optical coherence tomography

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Abstract. – OBJECTIVE: To assess the effect of morbid obesity on retinal nerve fiber layer (RNFL) thickness, central macular thickness (CMT), retinal ganglion cell (RGC), choroidal thickness (CT), central corneal thickness (CCT), and intraocular pressure (IOP).

PATIENTS AND METHODS: Sixty-seven patients defined as having morbid or class III obesity (BMI ≥ 40; Group 1) scheduled to undergo sleeve gastrectomy surgery and 29 nonobese patients (BMI 18.50-24.99; Group 2) underwent complete ophthalmic examination for measurement of IOP, CT, RNFL thickness, CMT, RGC, and CCT. RNFL thickness, CMT, and RGC were measured using spectral-domain optical coherence tomography (SD-OCT). CT measurement was performed using the enhanced depth imaging technique of the SD-OCT. The group data were analyzed and compared using the Mann-Whitney U test and Student's t-test. The relationship between the clinical ocular variables and obesity was analyzed using the Spearman's rank correlation test.

RESULTS: The mean IOP and CCT of Group 1 were found to be significantly higher ($p < 0.001$) and the mean RNFL, RGC, and CT significantly lower ($p < 0.05$) than those of Group 2. While Group 2 was found to have a slightly larger cup-to-disc ratio and Group 1 to have a thinner CMT, the differences between Groups 1 and 2 regarding these variables were not found to be statistically significant ($p = 0.322$ and $p = 0.072$, respectively). The results of Spearmen correlation analysis indicated the existence of a moderately positive correlation between IOP and BMI ($p < 0.001$; r = 0.5-0.6).

CONCLUSIONS: We have demonstrated by SD-OCT that morbid obesity may have a significant influence on RNFL, RGC, and CT. Morbid obesity may induce inflammatory, hormonal, and metabolic changes.

Key Words:
Intraocular pressure, Retinal nerve fiber layer, Choroidal thickness, Morbid obesity.

Introduction

Obesity and morbid obesity are common diseases with a high prevalence that continues to increase globally. Both are serious conditions associated with significant morbidity and mortality and a complex etiology attributed to a complex of genetic and environmental factors. Diagnosis of obesity and morbid obesity are based on calculation of body mass index (BMI), which is calculated as weight/height^2 (kg/m^2). The World Health Organization defines underweight as a BMI ≤ 18.50, normal weight as a BMI 18.50-24.99, overweight as a BMI 25.00-29.99, obese class I as a BMI 30.00-34.99, obese class II as a BMI 35-39.99, and obese class III or morbidly obese as a BMI ≥ 40[1]. Morbid obesity is also defined as a BMI ≥ 35 kg/m^2 with concomitant health problems or ≥ 40 kg/m^2 without concomitant health problems.

Obesity is known to have detrimental effects on the cardiovascular and metabolic systems and is thus a strong risk factor for diabetes mellitus, hypertension, cardiovascular disease, stroke, and sleep apnea syndrome[2]. Although the effect of obesity on the eye has not been well documented, it has been associated with cataracts, glaucoma, diabetic retinopathy, and age-related maculopathy[3].

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Spectral-domain optical coherence tomography (SD-OCT) is a technique used to acquire high-resolution cross-sectional scans of the retina choroid and retinal nerve fiber layer (RNFL). New-generation SD-OCT is a noninvasive means of collecting detailed information on the retinal microstructure, allowing for early detection of subclinical retinal changes at the microvascular level. The detection of such changes may provide a better understanding of the pathophysiological mechanisms of posterior segment eye diseases[4].

Despite the increasing prevalence of obesity and its associated complications, to our knowledge no study has investigated the effect of morbid obesity on intraocular pressure (IOP), choroidal thickness (CT), RNFL thickness, central macular thickness (CMT), and retinal ganglion cell (RGC), and central corneal thickness (CCT) and the relationship between these ocular factors and morbid obesity. To fill this study gap, we measured IOP, RNFL, RGC, CMT, CCT and CT in individuals with morbid obesity and compared the measurements that we obtained from age- and sex-matched nonobese individuals.

Patients and Methods

Patients

The study protocol was approved by the local Ethics Committee of Antalya Training and Research Hospital (Number: 2013/180) and Informed Consent was obtained from all participants included in the study. The research adhered to the tenets of the Declaration of Helsinki and all subjects signed a detailed written informed consent form prior to participation in the study. The study sample was composed of two groups. Group 1 was composed of 67 patients defined as having morbid or class III obesity (mean BMI 49.15 ± 7.65 kg/m^2) who volunteered for participation out of a group of 220 morbidly obese patients scheduled to undergo sleeve gastrectomy surgery at the General Surgery Department of the Antalya Training and Research Hospital. Group 2 was composed of 29 age- and sex-matched nonobese individuals with BMI values between 18.50 and 24.99 (mean BMI = 22.99 ± 1.89 kg/m^2). The participants' weight and height were measured using the same device to ensure equivalence in comparison. The blood pressure values ranged from 110/80 mm Hg to 130/90 mm Hg. The inclusion criteria for all subjects were best-corrected visual acuity of 20/20 or more and refractive errors between +1 D and -1 D spherical equivalent. The exclusion criteria were morbid obesity with other endocrine disorders; history of smoking or alcohol consumption; history of ocular surgery, laser therapy, ocular trauma, or anterior or posterior segment disease; use any medication within the previous three months; strabismus; amblyopia; IOP > 21 mmHg; or glaucomatous findings (e.g., glaucomatous optic disc changes or visual field defects).

Measurement

All patients underwent a detailed ophthalmic examination that included visual acuity testing; refraction assessment; anterior segment slitlamp biomicroscopy; fundus examination; IOP measurement using a Goldmann applanation tonometer; CCT measurement using ultrasonic pachymetry (Nidek UP-1000; Nidek Co., Ltd., Gamagori, Aichi, Japan). Using the values obtained, the CCT-adjusted IOP value was calculated. RNFL, CMT, cup-to-disc ratio, and RGC assessment using SD-OCT (Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA, USA).

CT measurements were performed by the same experienced retinal specialist blind to the patients' BMI using a high-speed and high-resolution SD-OCT device. CT was measured perpendicularly from the outer edge of the retinal pigment epithelium to the choroid-sclera boundary at the fovea using a single line of 6-mm length centered horizontally on the fovea for visualization of the choroid. The TruTrack active eye tracking system, which enables the capture of multiple images in the same location, and the automatic real-time mean function, which combines these images, were used during each image acquisition. All measurements were performed between 9:00 and 11:00 to avoid diurnal fluctuations.

Statistical Analysis

Statistical analysis was performed using the statistical package SPSS v 22.0 (SPSS Inc., Chicago, IL, USA). Data were analyzed by Mann-Whitney *U* test and Student's *t*-test. The relationship between clinical measurements was analyzed by Spearman's rank correlation test. The p-value < 0.05 was considered an indication of statistically significant.

Results

The demographic and clinical characteristics of the study sample and the statistical significance of the differences between the study groups are shown in Table I. The mean IOP, RNFL, CMT, RGC, CT, and CCT of Group 1 were 17.71 ± 2.56 mmHg, 94.88 ± 12.12 μm, 240.99 ± 21.47 μm, 82.31 ±7.16 μm, 300.63 ± 65.55 μm, and 557.33 ± 28.77 μm, respectively. The mean IOP, RNFL, CMT, RGC, CT, and CCT of Group 2 were 13.50 ± 1.59 mmHg, 99.55 ± 7.05 μm, 249.38 ± 18.82 μm, 86.41 ± 7.01 μm, 338.79 ± 64.41 μm, and 540.03 ± 25.88 μm, respectively. The mean IOP and CCT were found to be significantly higher ($p < 0.001$) and the mean RNFL, RGC, and CT significantly lower ($p < 0.05$) in Group 1. While Group 2 had a slightly larger cup-to-disc ratio and Group 1 had a thinner CMT, the differences between Groups 1 and 2 regarding these variables were not found to be statistically significant ($p = 0.322$ and $p = 0.072$, respectively). The results of Spearman correlation analysis indicated the existence of a moderately positive correlation between IOP and BMI ($p < 0.001$; $r = 0.5$-0.6).

Discussion

Obesity is a major public health problem with a prevalence increasing at remarkable rates in many countries. Obesity results from morphological and functional changes in the adipose tissue associated with changes in various inflammatory, endocrine, hormonal (changes in leptin and ghrelin levels), and metabolic factors[4,5]. Several possible pathophysiological mechanisms have been proposed to explain the association between morbid obesity and ocular diseases. One prominent theory is that obesity induces changes in plasma levels of leptin, which is secreted by adipose tissue, and ghrelin, both of which play an important role in the pathophysiological mechanisms linking obesity with glaucoma[6-8]. In support of this theory, studies have found that many individuals with obesity have hyperleptinemia[6]. In accordance by this finding, recent research has found that oxidative stress in obese individuals may increase as a result of hyperleptinemia, which may trigger pathological changes leading to elevated IOP[9,10].

Recent research has revealed that ghrelin, a hormone with a 28-amino acid lipopeptide structure that is known to have various anti-inflammatory and antioxidant effects, plays an important role in the anterior and posterior segments[11]. Alvarez-Castro et al[11] and Kojima et al[12] have found that plasma ghrelin levels are lower in morbidly obese individuals compared to nonobese individuals, while Katsanos et al[7] showed that ghrelin levels in the anterior chamber of patients with glaucoma were significantly lower than levels in controls. Moreover, Rocha-Sousa et al[13] detected ghrelin mRNA in the non-pigmented ciliary epithelium and the posterior surface of the iris. While RCGs exhibit high sensitivity to increased IOP levels, ghrelin has been shown to have protective effects on RGCs. In accordance by these findings, Can et al[8] found that ghrelin has antioxidant and neuroprotective effects on the retina in an experimental glaucoma model.

Several studies that have investigated the relationship between BMI and IOP have found a significantly positive correlation. Among them, Klein et al[14] demonstrated that a rise in BMI val-

Table I. Demographic and clinical characteristics of the study groups.

	Group 1 (n = 67)	Group 2 (n = 29)	p
Age, years	37.92 ± 9.82	35.31 ± 7.93	0.066
BMI# (kg/m^2)	49.15 ± 7.65	22.99 ±1.89	< 0.001*
IOP+ (mmHg)	17.71 ± 2.56	13.50 ± 1.59	< 0.001*
RNFL+ (μm)	94.88 ± 12.12	99.55 ± 7.05	0.020*
C/D#	0.37 ± 0.19	0.40 ± 0.16	0.322
CMT+ (μm)	240.99 ± 21.47	249.38 ± 18.82	0.072
CCT+ (μm)	557.33 ± 28.77	540.03 ± 25.88	0.006*
CT+ (μm)	300.63 ± 65.55	338.79 ± 64.41	0.036*
RGC# (μm)	82.31 ± 7.16	86.41 ± 7.01	0.03*

BMI: body mass index; IOP: intraocular pressure; RNFL: retinal nerve fiber layer; C/D: cup-to-disc ratio; CMT: central macular thickness; CCT: central corneal thickness; CT: choroidal thickness; RGC: retinal ganglion cell. #Analyzed with the Mann-Whitney U test. +Analyzed with the Student's t-test. *$p < 0.05$.

ues is associated with a parallel increase in IOP, Mori et al[15] found that BMI was significantly correlated with IOP, and Akinci et al[16] identified a positive correlation between IOP and obesity (mean BMI of study group = 36 kg/m^2). In contrast, Albuquerque et al[17] found no correlation between BMI and IOP in children (mean BMI = 29.7 kg/m^2). These findings suggest that obesity is an independent risk factor for the increase in IOP and thus support the first proposed theory[15].

The second theory proposes that vascular and mechanical factors associated with the etiology of glaucoma may both be rooted in obesity-related changes[3,18]. An increase in intraorbital adipose tissue decreases the episcleral aqueous outflow, thus leading to an increase in IOP[18]. In support of this theory, Stojanov et al. showed that obese individuals have significantly higher volumes of retrobulbar adipose tissue and that this higher volume is positively correlated with higher IOP[19]. Obesity also increases the blood red cell count, which raises blood viscosity and reduces episcleral aqueous outflow[20]. Elevated blood pressure raises ciliary artery pressure, which in turn increases aqueous humor filtration. Hyperglycemia, on the other hand, may cause osmotic fluid shift into the intraocular space[21].

The third theory, which supports Boillot et al[22] finding that obesity has a significant effect on the human microcirculation, proposes the existence of a relationship between BMI and nitric oxide (NO), an endothelium-derived vasodilator molecule. As NO acts as an important mediator regulating ocular blood flow and positively affects IOP regulation, it is hypothesized to play an important role in the pathogenesis of glaucoma[23]. Several studies support this hypothesis. Stapleton et al[24] found that obese individuals have decreased levels of NO, which could result in impaired dilatation of the vasculature. Kamide et al[25] identified a positive association between levels of vasoconstrictor molecules, such as endothelin-1(ET-1) and angiotensin-II (Ang-II), and BMI. Choritz et al[26] found a highly significant correlation between IOP and ET-1, which is observed in increased concentrations in the aqueous humor of glaucoma patients. ET-1 might be associated with the reduction of blood flow to the optical nerve heads and the loss of cells in the retinal ganglion, a vascular phenomenon that might compromise optic nerve perfusion[27,28]. In a rabbit model, Gherghel et al[29] found that intracameral administration of Ang-II reduced uveoscleral outflow and that intravitreal administration of Ang-II increased resistance to aqueous humor drainage. Based on these findings, it is plausible to hypothesize that in morbid obesity, changes in levels of hormones (i.e., increases in leptin levels and decreases in ghrelin levels), vasodilators (i.e., decreases in NO levels), and vasoconstrictors (i.e., increases in ET-1 and Ang-II); induction of neurotoxicity; decrease in blood flow; ocular vascular dysregulation; mechanical factors; and oxidative stress may all play an important role in the progression of glaucoma and ocular disease[20,29,30].

In the current study, we found that the nonobese subjects had a slightly larger cup-to-disc ratio than the morbidly obese subjects but that the difference in this ratio between the two groups was not statistically significant (p=0.322). The results of previous studies regarding the relationship between cup-to-disc ratio and obesity have been mixed. While Pedro-Egbe et al[31] found no association between obesity and vertical cup-to-disc ratio, Xu et al[32] found a significantly positive correlation between neuroretinal rim area and BMI. In the Singapore Malay Eye Study, Zheng et al[33] found that tall subjects with a low BMI had a small neuroretinal rim area as well as a wide cup-to-disc ratio. Likewise, Amerasinghe et al[34] reported larger cup-to-disc ratio as being significantly associated with lower BMI.

A precise clinical understanding of choroidal morphology is important for delineating the pathogenesis of many retinal and choroidal diseases. Previous studies of the mean subfoveal CT in healthy subjects reported a range from 241 to 372 □m[35]. Maul et al[36] demonstrated that glaucoma patients with low ocular perfusion pressure had decreased CT. In accordance, recent clinical studies have found significantly decreased CT in patients with pathologic myopia, age-related macular degeneration, glaucoma, and diabetic retinopathy. Contrary to retinal and optic nerve head vasculature, choroid vessels are subjected to autonomic regulation. Choroidal blood flow is reduced through sympathetic efferent nerve activation and the release of noradrenalin. On the other hand, the parasympathetic efferent nerves increase choroidal blood flow through NO signaling[37]. As an important mediator, NO plays a significant role in the modulation of ocular blood flow. This role is significant in understanding the effect of obesity on CT, as lower levels of NO have been found in morbidly obese patients. This finding, together with the positive association identified between BMI and levels of vasocon-

strictor molecules such as ET-1 and Ang-II, explains how the disruption of the vasodilator and vasoconstrictor balance (decreases in NO levels and increases in ET-1 and Ang-II levels) as a result of morbid obesity can affect CT. In accordance by Yilmaz et al[38], who showed that BMI was negatively correlated with CT, we found that the CT of the morbidly obese subjects was statistically thinner than that of the non-obese subjects.

Glaucoma-related alterations in the layers of the retina include the reduction of the number of ganglion cells and reduced thickness of the RNFL. It is possible that the ganglion cell loss (decreases in ghrelin and increases in ET-1) observed in morbidly obese patients might be due to a decrease in the thickness of the ganglion cell layer. To examine this possibility, we investigated the clinical parameters relevant to glaucoma diagnosis, including RNFL thickness, ganglion cell thickness, and vertical cup-to-disc ratio, in morbidly obese patients (mean BMI = 49.15 kg/m^2). To our knowledge, this study was the first to investigate all these parameters in the same samples of morbidly obese and nonobese subjects. We found that IOP and CCT were significantly higher while RNFL thickness, RGC, and CT were significantly lower in the morbidly obese group. The results of Spearman correlation analysis revealed the existence of a moderately positive correlation between IOP and BMI.

Conclusions

Our findings indicate that morbid obesity may have a significant effect on RNFL thickness, RGC, and CT. As thinner RNFL, decreased RGC, and decreased CT in morbidly obese individuals might increase their susceptibility to glaucoma and other retina- and choroid-related diseases, they thus suggest the need for more frequent measurement of IOP in these individuals for the earlier detection of glaucoma. It is now necessary to further investigate how weight loss following surgery affects OCT parameters and IOP in morbidly obese patients who undergo sleeve gastrectomy surgery.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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