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ORIGINAL CONTRIBUTIONS

Retinal Nerve Fiber Layer Thickness Decrease in Obesity as a Marker of Neurodegeneration

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Abstract

Background Idiopathic intracranial hypertension (IIH) is a serious condition that is frequently associated with irreversibly vision loss, having a higher incidence among obese women. Our aims were to screen subclinical IIH in obese patients scheduled to bariatric surgery using peripapillary retinal nerve fiber layer (RNFL) thickness and to evaluate if the findings demand the possible need of a preoperative evaluation in this population.

Methods This study included 111 eyes from 36 obese patients (86% female, body mass index > 35 kg/m^2) scheduled to bariatric surgery and 20 non-obese (body mass index < 25 kg/m^2) age-matched controls. We measured sectorial and mean RNFL thickness in a 3.5-mm-diameter circular scan centered on the optic nerve head, using optical coherence tomography (Heidelberg Spectralis SD-OCT) in all participants. Multivariate linear regression was used for adjustments.

Results No patient had subclinical IIH corresponding to increased RNFL thickness. However, in obese individuals, global peripapillary RNFL was thinner than in controls (104 ± 6 μm versus 99 ± 12 μm, $p = 0.005$). Overall, RNFL thickness was superior in the control group for all sectors. The differences reached significance for the nasal, temporal, superior temporal, and inferior temporal sectors. These differences remained even after adjusting for possible confounders (hypertension, dyslipidemia, diabetes, age, sleep apnea syndrome, and sex).

Conclusions Routine screening asymptomatic obese patients undergoing bariatric surgery for IIH using RNFL thickness was not clinically relevant in our study. However, we found that severe obesity is associated with neurodegeneration independently of the other components of the metabolic syndrome, what may justify future investigation on the need of monitoring these patients.

Keywords Peripapillary retinal nerve fiber layer · Obesity · Intracranial hypertension · Neurodegeneration

Introduction

Obesity has emerged as one of the highest current concerns on populational health. Its health and economic burden have led to the inclusion of adiposity among the global non-communicable disease targets [1].Globally, the proportion of adults with a body mass index (BMI) of 25.0 or greater increased from 28.8% in 1980 to 36.9% in 2013 for men and from 29.8 to 38.0% for

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women, in both developed and developing countries [2]. According to a World Health Organization (WHO) report, in 2014, 11% of men and 15% of women aged 18 years and older were obese worldwide [1]. In Portugal, the estimated prevalence of obesity is even higher: 22.3%, being significantly superior in women [3].

Obesity has well-known associated health consequences, with long-lasting effects on morbidity, such as increased risk of diabetes, cardiovascular diseases, and cancer [4], but also has established effects in the eye [5]. In fact, obesity is a major risk factor for idiopathic intracranial hypertension (IIH), a condition of increased intracranial pressure of unknown cause that often produces papilledema and permanent vision loss in up to 30% of patients [6]. IIH occurs most typically in obese women in their childbearing years and few risk factors are known beyond the increased weight [7]. It has been described that incidence rates of IIH have risen from 1.0/100000 (1990–2001) to 2.4/100000 (2002–2014) in parallel with trends of obesity [8], and it is predictable that more cases will occur with the continue epidemic of overweight worldwide [9]. These new trends may justify the need of re-evaluating the incidence of IIH in an era of increasing obesity.

Besides being the group at the highest risk for IIH, obese women also constitute most of worldwide candidates to bariatric surgery. In a study including 145,527 patients who underwent a bariatric procedure, 77.7% were women (mean age of 44.6 ± 12.1 years) [10]. It is also estimated that as many as 25% of patients with IIH may be asymptomatic [11], and it appears that those with severe obesity have worse visual outcomes [6]. Therefore, we hypothesize that IIH may be underdiagnosed in patients undergoing bariatric surgery and that asymptomatic obese patients (namely female) may be at higher risk for vision loss.

The retinal nerve fiber layer (RNFL), the innermost retinal neural layer, primarily contains the axons of retinal ganglion cells, most of which synapse in the lateral geniculate nucleus. Because of their unmyelinated nature, measuring the thickness of this layer provides valuable information for evaluation of central nervous system [12]. Optical coherence tomography (OCT) is a non-invasive and noncontact imaging tool for the quantification of RNFL thickness. RNFL increases have shown to early detect IIH in a non-invasive way, also enabling the monitoring of responses to treatment [13]. This is particularly relevant, as in the case of mild papilledema fundoscopy findings may sometimes be insufficient leading to false and misleading indices in the diagnosis of early-stage disease [14].

In this study, we aimed to screen IIH in asymptomatic obese patients scheduled to bariatric surgery by measuring RNFL thickness, and to evaluate if the findings demand the possible need of a preoperative screening in this population.

Methods

This is a prospective study that was conducted in two Portuguese Reference Centers for Obesity Treatment (Centro Hospitalar de São João, Porto, Portugal and Centro Hospitalar de Entre o Douro e Vouga, Santa Maria da Feira Portugal). All procedures were performed in accordance with the ethical standards of the Hospital Ethics Committees and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Sampling

Participants were prospectively recruited from January 2018 to July 2018. Patients that were proposed to bariatric surgery after multidisciplinary evaluation were consecutively invited to participate in the study. Body mass index (BMI) was determined using the formula weight (kg)/height^2 (m^2). We only included patients with BMI > 35 kg/m^2(severe/morbid and super obese patients) with no previous systemic disease besides hypertension, diabetes, dyslipidemia, or obstructive sleep apnea.

Controls consisted in consecutive non-obese (BMI ≤ 25 kg/m^2) healthy volunteers, age-matched, and with no ocular or systemic disease besides hypertension, diabetes, or dyslipidemia.

Individuals were excluded in both groups if they had a personal or familial history of glaucoma or ocular hypertension, uveitis, optic neuropathy, diabetic retinopathy, age-related macular degeneration, vitreoretinal, optic nerve or choroidal vascular diseases, refractive error corresponding to spherical equivalent of more than 6/− 6 diopters, recent history of decreased visual acuity, previous refractive or intraocular surgery, narrow anterior chamber angle, and secondary causes of glaucoma, such as syndrome of pigment dispersion and pseudoexfoliation syndrome.

Sample size was estimated to detect a minimal difference in RNFL thickness between obese and non-obese patients of 10 μm, assuming a standard deviation of 10 μm and a ratio of 2 cases/1 control. Using these criteria, at least 12 controls and 24 cases were used as reference sample size.

Measurements

Heidelberg Spectralis spectral-domain optical coherence tomography (SD-OCT, Heidelberg Engineering, Heidelberg, Germany) was employed to assess RNFL thickness. A 256 A-scan image with 3.5-mm diameter circular rings (Fig. 1a), centered on the optic nerve were acquired, and the mean value was expressed as RNFL thickness. Each image was reviewed in a masked fashion. To enhance accuracy, if necessary,

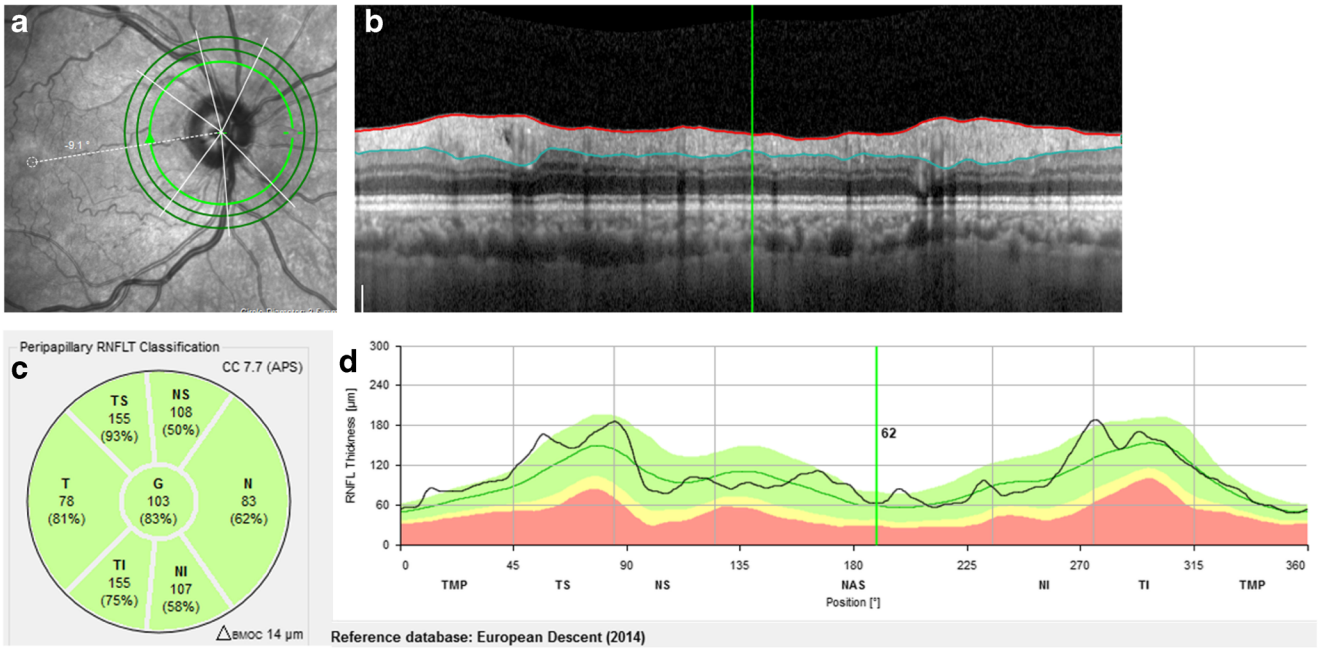

Fig. 1 The figure describes the process of measuring retinal nerve fiber layer (RNFL) thickness in one random eye. Optical coherence tomography (OCT) is a technology that provides RNFL thickness values at a fixed distance away from the optic nerve (approximately 3.5 mm diameter, circular, cross-sectional thickness centered around the optic nerve)(**a**). OCT measures and quantify RNFL thickness by calculating the area between the internal limiting membrane (ILM) and RNFL border (**b**). RNFL data is extracted to create a map with a global value and six sectors (temporal, superior, nasal, inferior, temporal) (**c**, **d**).It is displayed as a color scale with the thickness values referenced to a normative database (in this case, European)

segmentation lines were adjusted (Fig.1b), and non-centered or images with poor quality were discarded. RNFL measurements (μm) were recorded as global and six regional (temporal, temporal superior, nasal superior, nasal, nasal inferior, and temporal inferior) sectors (Fig.1c,d). Both eyes from the same participant were inputted for analysis.

Data on hypertension, diabetes or dyslipidemia and existing obstructive sleep apnea syndrome were also collected. As all obese patients go under a routine endocrinology evaluation before surgery, data on these comorbidities was confirmed using serum evaluations.

Statistical Analysis

Statistical analysis was performed using SPSS (25.0, SPSS Inc. Chicago, USA) and significance was set at 0.05. Continuous variables were expressed as mean ±standard deviation or as median (interquartile range), and categorical variables as frequency and percent. Continuous variables were compared using independent *t*test or Mann-Whitney test. Categorical variables were compared using Fisher test. A linear regression model was used to adjust the relationship between obesity and RNFL thickness to possible confounders. Variables that were included in the model were hypertension, dyslipidemia, diabetes, age, sleep apnea syndrome, and sex.

Results

In total, 111 eyes from 56 patients were included (36 in the obese group, 20 controls). The median age was 50 ± 10 years and 18% were male. Clinical and demographic variables for both groups are detailed in Table 1. We excluded one eye from the analysis because of poor SD-OCT image quality, due to corneal opacities.

We did not verify any case of subclinical increased peripapillary RNFL thickness in the obese group. By contrast,

Table 1 Clinical and demographic characteristics

Variables	Obese group ($n = 36$)	Controls ($n = 20$)	p value
Male (n, %)	5 (14)	5 (25)	0.2*
Age (years)	49 ± 9	53 ± 11	0.07¥
Mean BMI (kg/m^2)	44 ± 6	23 ± 2	< 0.001¥
BMI Range (kg/m^2)	35–59	17–25	
Diabetes (n, %)	17 (47)	2 (10)	< 0.001*
Hypertension (n, %)	19 (53)	7 (35)	0.16*
Dyslipidemia (n, %)	15 (42)	5 (25)	0.14*
OSA (n, %)	9 (25)	0 (0)	< 0.001*

Continuous data are presented as mean±standard deviation or as median (range). *OSA* obstructive sleep apnea,*BMI* body mass index, *Fisher's Exact Test. ¥ Independent *t* test

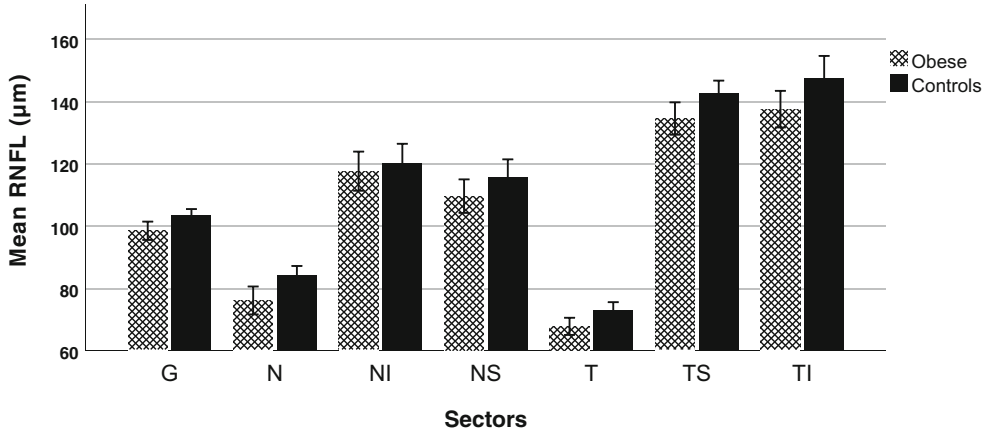

Fig. 2 Peripapillary retinal nerve fiber layer (RNFL) thickness by sectors and group. G, global; N, nasal; NI, nasal and inferior; NS, nasal and superior; T, temporal; TS, temporal and superior; TI, temporal and inferior

global RNFL thickness was decreased in the obese group when compared to controls (mean 104 ± 6 μm versus mean 99 ± 12 μm, $p = 0.005$). Figure 2 describes RNFL thickness in both groups by sectors. Overall, RNFL thickness was superior in the control group for all sectors. The differences reached significance for the nasal, temporal, superior temporal, and inferior temporal sectors.

Using a liner regression model, we verified that the relationship between global peripapillary RNFL thickness and severe obesity remained even after adjusting for possible confounders (confounders included hypertension, dyslipidemia, diabetes, age, sleep apnea syndrome, and sex; $B = 7.5$, CI95% 2.7–12.5; $p = 0.003$). The same was verified for the nasal sector ($B = 7.9$, CI95% 0.37–15.5; $p = 0.04$), temporal sector ($B = 7.5$; CI95% 2.5–12-5; $p = 0.004$), superior temporal sector ($B = 9.6$, CI95% 0.5–18.7; $p = 0.03$), and inferior temporal ($B = 19.2$; CI95% 8.8–29; $p < 0.001$).

Discussion

In this study, no patient had subclinical increase of RNFL thickness reflecting subclinical IIH. Impaired axoplasmic flow, secondary to increased intracranial pressure and increased perineural pressure, causes optic disc swelling, and its importance reflects in the possibility associated permanent vision loss [13, 14]. The only factors that have been consistently associated with IIH are increased weight and female sex [6, 7]. It has been established that until 25% of patients with IIH are asymptomatic [11], and this number may be underestimated with the increasing prevalence of obesity in the recent years [9]. Therefore, it is important to investigate obese patients, namely those with severe obesity (that are at higher risk of having worse visual outcomes), so that we can exclude subclinical disease. As most candidates for bariatric surgery are obese women [10], we can hypothesize that this is an extremely high-risk population for IIH development. RNFL thickness increases can detect IIH early in its course [13, 14], even in cases with absent papilledema. Because of the exposed, we aimed to evaluate if the possible presence of subclinical increases in RNFL thickness in a random population of obese patients undergoing bariatric surgery may justify their preoperative screening, and we found no subclinical changes that may justify such a strategy. We must highlight that IIH has a relatively low prevalence in general population. Much of the knowledge on the incidence of IIH came from the Rochester Epidemiology Project (REP), which demonstrated an incidence of 1.0 per 100,000 from 1976 through 1990 [15]. However, few studies have documented this prevalence recently in severely obese woman. As IIH is a condition of unknown etiology with unpredictable occurrence, determining screening strategies among high-risk groups is essential to avoid further visual deterioration.

Contrary to what was expected, we detected decreased RNFL thickness in obese patients when compared to healthy controls. Notably, this decrease was significant globally, and in the nasal, temporal, temporal superior, and temporal inferior sectors. We also concluded that, in our sample, obese patients had decreased RNFL thickness independently of age, sex, and comorbidities that are frequently associated with obesity (dyslipidemia, diabetes, hypertension, and sleep apnea syndrome).

The relationship between BMI and glaucomatous neuropathy has been controversial. Bonomi et al. [16], Vijaya et al. [17], and Yamamoto et al. [18] conductedlarge populational studies and found no relationship between BMI and open-angle glaucoma. In the Central India Eye and Medical Study, Nangia et al. [19] found that lower BMI (per unit) was associated with primary open-angle glaucoma. Similarly, in the 9-year longitudinal evaluation of Rotterdam

Eye Study, Ramdas et al. [20] observed that individuals with lower BMI (per unit) at baseline were 6% more likely to develop primary open-angle glaucoma. By contrast, Khawaja et al. [21] concluded that higher BMI was associated with a thinner RNFL in men only. However, besides reporting controversial results, these studies had a low representation of obese patients as it was not an inclusion criterion, and we cannot directly infer about that subgroup through them. Recently, Zarei et al. [22] described for the first time that the metabolic syndrome was associated with eye neurodegeneration, and that RNFL thickness was significantly reduced in participants with higher numbers of metabolic abnormalities, independent of age, gender, and the side of the examined eye. In this study, they considered groups based on presence/absence of metabolic syndrome criteria, and they did not include the obese/non-obese variable as a criterion in the final model, so, again, the direct effect of obesity in neurodegeneration was not explored. Other previous studies have also suggested the retinal neurodegeneration in the various components of the metabolic syndrome separately, irrespective of weight [23, 24]. In our study, however, we found decreased RNFL thickness in obese patients compared to healthy controls, concluding that this decrease was independent of other components of the metabolic syndrome mentioned above, suggesting that marked overweight per se may be a risk factor for neurodegeneration processes. To our knowledge, only Dogan et al. [25] performed a similar analysis, but including patients with BMI > 40 kg/m^2, and they also found decreased global RNFL thickness compared to a control group, but did not detailed peripapillary quadrant differences.

Aging accompanies RNFL thinning, and it is estimated that RNFL thickness decreases by 2.0 μm per decade of age [26]. Development of obesity has been shown to accelerate the aging process [22, 27]. Obesity has, inclusively, been associated with brain neurodegenerative disorders, that may explain our findings [28]. A previous study suggested that visceral fat accumulation and a reduction in lipoprotein lipase activity may induce neurodegenerative retinal disorders and a subsequent decline in RNFL thickness [29]. Other studies have demonstrated that high adiposity (fat) levels are associated with an environment of chronic low-grade inflammation, which may contribute to neurological disorders through elevated levels of inflammatory cytokines, such as IL-6, IL-1β, and TNFα [26, 30, 31]. The measurements of RNFL, the innermost retinal neural layer, provide valuable information for the evaluation of central nervous system [12]. In our study, the neurodegeneration that was found in the optic nerve is probably a marker for the systemic neurodegeneration that our patients had. The relationship between obesity and neurodegeneration appears to be complex, and further studies in this area may elucidate the biological routes implied in neurodegeneration in these patients. Additionally, the potential of bariatric surgery in reverting the features of neurodegeneration must also be elucidated.

Our study has some limitations. Regarding IIH, we know that this is a low prevalence condition and that our study is limited by the sample size. However, as we just wanted to detect if a subclinical increase in RNFL thickness was as frequent as it may justify a routine preoperative screening, and larger samples would not improve our conclusions. Regarding neurodegeneration, as it was not our primary aim, we did not evaluate the visual fields. The functional relevance of a thinner RNFL should be analyzed in future studies using visual field testing. Secondly our sample was constituted of a higher number of females. Although this is an advantage as obese females are the highest risk group for intracranial hypertension, and this was our main aim; future studies may address neurodegeneration considering homogeneous cohorts. Additionally, we evaluated extreme groups: whether patients with BMI < 35 kg/m^2 also experience signs of early neurodegeneration or it is an effect of extreme obesity has yet to be determined.

Despite these potential limitations, this study demonstrates a direct assessment of RNFL thickness in obese patients. No subclinical IIH cases were detected justifying routine preoperative screen in patients undergoing bariatric surgery. However, obesity was associated with neurodegeneration independently of the other components of the metabolic syndrome. Although these findings do not demand an urgent ophthalmologic evaluation in all obese patients that undergo bariatric surgery, only the prospective monitoring of the visual function (using visual fields, for instance) will demonstrate the impact of long-term deterioration. Further studies may also evaluate the potential of preventive strategies regarding weight loss in delaying the neurodegenerative process.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent Informed consent was obtained from all individual participants included in the study.

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