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Research article

Relations of Macular Variability with Anthropometric Measurements, Metabolic Parameters and Inflammatory Markers in Children and Adolescents with Metabolic Syndrome: A Cross-Sectional Study

Short running title: Metabolic Syndrome and macular variability

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What is already known on this topic?
Obesity and MetS is capable of causing damage in several organ systems, and also microangiopathic changes, retinal degeneration, optic nerve function impairment, and damage in the choroid and macular regions in the eye, by triggering a chronic subclinical inflammatory process. Optical coherence tomography may show early macular damage.

What this study adds?
This is the first study to show that macular retinal thickness and macular retinal volume values decrease as body mass index standard deviation scores (BMI-SDS) and waist circumference standard deviation scores (WC-SDS) increase in obese children and adolescents with metabolic syndrome as evidence of macular damage. The increases in neutrophil/lymphocyte ratio, the platelet/lymphocyte ratio and the systemic immune-inflammatory index may be a marker of chronic inflammation in children with metabolic syndrome, and are associated with macular damage.

Abstract:
Background: Macular damage may be observed in obesity and metabolic syndrome (MetS) that lead to chronic subclinical inflammation and affect almost all organ systems.
Objectives: The purpose of this study was to investigate the relations of macular variability with anthropometric measurements, metabolic parameters, and inflammatory markers in children and adolescents with MetS.

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Methods: Two hundred twenty-eyes of 62 obese and 48 healthy children and adolescents were included in the study. Bilateral macular retinal thickness (MRT) and macular retinal volume (MRV) were measured in all subjects using optical coherence tomography (OCT). Relations between mean MRT and MRV and age, auxological measurements, metabolic parameters and the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), and the systemic immune-inflammatory index (SIII) were investigated.
Results: No statistically significant difference was observed between the groups in terms of age, sex distribution ($p>0.05$). Mean MRT ($r= -0.326$, $p=0.007$) and MRV ($r=-0.303$, $p=0.007$) values in the obese group with MetS decreased as homeostasis model assessment insulin resistance (HOMA-IR) values increased. SIII values were higher in obese groups, but particularly in the obese subject with MetS, compared to the control group ($p=0.021$). The decrease in mean MRT ($r= -0.544$, $p= 0.046$) and MRV ($r= -0.651$, $p=0.031$) in the obese subjects with MetS was negatively correlated with NLR. Mean MRT and MRV decreased in all obese subjects as SIII increased ($p<0.05$).
Conclusion: This is the first study to show that mean MRT and MRV values decrease as body mass index standard deviation scores (BMI-SDS) and waist circumference standard deviation scores (WC-SDS) increase in obese children and adolescents with MetS. NLR and SIII may be a marker of chronic inflammation in obese children with MetS and are associated with macular damage.
Key words: Macular retinal thickness, macular retinal volume, metabolic syndrome, optical coherence tomography, pediatric obesity.

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Introduction

The prevalence of obesity and metabolic syndrome (MetS), which is a complication of obesity, is increasing. MetS is capable of causing damage in several organ systems, and also microangiopathic changes, retinal degeneration, optic nerve function impairment, and damage in the choroid and macular regions in the eye, by triggering a chronic subclinical inflammatory process (1,2). These changes can be identified in the early stages using optical coherence tomography (OCT). The layers of the eye can be visualized in a painless, rapid, and noninvasive manner with OCT (3). OCT is particularly used to visualize macular pathologies, such as diabetic macular edema, and macular degeneration (4-6).

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The macula is where detailed vision takes place and is of critical importance to the sense of sight. A deleterious impact on the macular region can cause progressive or permanent vision impairment. The macula can also be damaged in obesity and MetS that lead to chronic subclinical inflammation and affect almost all systems (7).
Complete blood count is an inexpensive and easily accessible test. The neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune-inflammatory index (SIII) that are easily calculated from complete blood count have been shown to indicate subclinical inflammation in several studies (8-10).

To the best of our knowledge, no previous studies have investigated the relations of macular retinal thickness (MRT) and macular retinal volume (MRV) changes with metabolic parameters, and inflammatory markers in children with MetS.
The purpose of this study was to use OCT to investigate variability in MRT and MRV between obese children and adolescents with MetS and without MetS and healthy controls as evidence of macular damage. This study also evaluated relations of changes in macular retinal measurements with anthropometric measurements, metabolic parameters, pubertal stage, and NLR, PLR and SIII which are the subclinical inflammation markers.

Materials and methods:

This prospective observational study commenced following receipt of institutional Medical Research Ethical Committee approval (2019/9-3), and was conducted in accordance with the ethical principles of the Declaration of Helsinki.
Patients aged 10-18 years, with no history of ocular disease or surgery, with no neurological diseases, and with spherical values between -0.75D and +0.75D were enrolled in the study and control groups. All children and their parents consented to examination.
Individuals with a history of ocular trauma and dense media opacities, using systemic corticosteroids, with diabetes mellitus or any systemic disease, or with acute/chronic local/systemic infectious disease, and children unsuitable for OCT measurement, were excluded.
One hundred twenty-four eyes of 62 obese children and adolescents with a range of 10.1 to 17.9 years presenting to the Izmir Tepecik Training and Research Hospital Pediatric Endocrinology Clinic, Turkey, between February 2016 and February 2019, and 96 eyes of 48 healthy children and adolescents with a range of 10.0 to 17.8 years, were included in the study. Informed consent was obtained from patients and their families.
Demographic data for all groups were elicited from the medical files. Body measurements, blood pressure values and pubertal stages were assessed by an experienced pediatric endocrinologist. Pubertal stages were classified based on the Tanner system (11). Height was measured to the nearest centimeter with a rigid stadiometer. All subjects were also weighed unclothed to the nearest 0.1 kg using a calibrated balance scale. Body mass index (BMI) was calculated using the formula weight (kg)/height (m^2). Standard deviation scores (SDS) for weight, height and BMI were calculated based on reference values established for Turkish children (12). Obesity was diagnosed based on World Health Organization criteria (13). Blood pressure was measured three times at 10-min intervals following a rest period. Systolic and/or diastolic blood pressure values exceeding the 95th percentile were regarded as hypertensive (14). Complete blood count, and blood glucose, insulin and serum lipids in the

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obese groups were measured from fasting venous specimens collected on the same day using an automatic analyzer. Insulin resistance using homeostasis model assessment (HOMA-IR) was calculated with the formula fasting insulin (μIU/mL) × fasting glucose (mg/dL)/405 (15). MetS was diagnosed based on International Diabetes Federation criteria (16). The syndrome was defined as two or more of hypertriglyceridemia (>150 mg/dl), decrease in HDL (<40 mg/dl), blood pressure elevation (systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 85 mmHg), or glucose metabolism disorder in the presence of abdominal obesity in cases aged 10-16 years. Adult criteria were used for the diagnosis of metabolic syndrome at the age of 16 years and over. Percentile curves established for Turkish children were used for waist circumference. A waist circumference of the 90th percentile or higher was regarded as central obesity (17). The online calculator program developed by Demir K et al. was used for all auxological measurements and blood pressure evaluation (18).

Three groups were established – healthy control (Group 1), MetS- obese (Group 2), and MetS+ obese (Group 3).

All cases underwent extensive ocular examination by the same ophthalmologist. This included best corrected visual acuity, detailed anterior segment examination with a slit-lamp biomicroscopy, intraocular pressure using a Goldman applanation tonometer, ocular motility examination, and optic nerve and retina examination with a 90 diopter lens. One percent cyclopentolate hydrochloride (Sikloplejin -Abdi İbrahim İlaç Sanayi, Istanbul. Turkey) eye drops were administered three times at 5-minutes intervals for pupillary dilatation. Measurements were recorded using an automated refractor (Topcon KR-1, Topcon, Tokyo, JAPAN) 30 minutes after the final drop administration. The mean value of the three measurements was recorded. Subjects with spherical values between -0.75 D and +0.75 D were enrolled in the study.

Retinal thickness and volume in the macular region were measured using a Spectralis OCT device (Heidelberg Spectralis, Heidelberg Engineering, Heidelberg, Germany). All participants were asked to wait in a darkened room before measurement. All scans were carried out on a 20 X 20 degree cube with 49 raster lines at 120-μm intervals. Retinal thickness and volume in the macula were calculated automatically as the distance separating the vitreoretinal interface from the margin representing the junction of the photoreceptor inner and outer segments. The macula was divided automatically into three concentric 1-, 3-, and 6-mm rings. Retinal thickness and volume were measured on these three rings in accordance with the Early Treatment Diabetic Retinopathy Study Groups (ETDRS) macular map (19). The inner and outer rings were further divided into four quadrants (superior, temporal, inferior, and nasal) by two reticules.

The 1-mm ring was defined as the central circle, the 3-mm ring as the inner segment circle and the 6-mm ring as the outer segment circle. Ocular observation was performed automatically in real time. Measurements were taken from both eyes by two independent masked observers. In order to avoid diurnal fluctuations, all OCT images were taken between 10.00 and 12.00 hours. Total macular thickness and volume including all nine subfields were subjected to analysis.

The MRT and MRV values, and the means thereof, were subjected to statistical analysis and compared between the groups. In addition, correlation analysis was performed between mean MRT and MRV values and age, pubertal stages, body measurements, systolic/diastolic blood pressures, fasting insulin, HOMA-IR, lipid values, NLR, PLR, and SIII. SIII was calculated using the formula (platelet × neutrophil)/lymphocyte.

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Statistical analyses: Statistical analysis was performed on Statistical Package for Social Sciences (SPSS 20.0; IBM, USA) software. Normality of sample distribution was evaluated using the Kolmogorov–Smirnov test. Mean and standard deviation values were calculated for all parameters. Pearson correlation analysis was applied for normally distributed variables, and Spearman correlation analysis for non-normally distributed variables. $P < 0.05$ was considered statistically significant.

Results:

One hundred ten cases with a range of 10 to 18 years were examined in this study. MetS was determined in 45.1% (28/62) of the obese group, but in no members of the control group.

Mean ages were 13.5±3.5 years in the control group (Group 1, n=48), 13.8±2.9 in the MetS- obese subjects (Group 2, n=34), and 14.1±3.3 in the MetS+ obese subjects (Group 3, n= 28). No statistically significant difference was observed between the groups in terms of age, sex distribution, or pubertal stages ($p>0.05$).

BMI standard deviation score (SDS) (BMI-SDS) was 3.0±0.4 in the obese group and 0.5±0.4 in the control group ($p=0.000$). Fasting blood glucose values were within normal limits in both groups (control group 81.7±8.7 mg/dl, obese group 85.3±9.9 mg/dl, $p=0.65$). BMI-SDS and WC-SDS were significantly higher in the obese cases than in the control group ($p=0.000$). Morning fasting insulin and HOMA-IR values were also significantly higher than in the controls (obese and control group fasting insulin 20.6±10.8 vs 8.3±3.1 mIU/ml, respectively, $p=0.02$, and HOMA-IR: 4.7±2.7 vs 1.8±0.8, respectively, $p= 0.01$). There was no difference in serum lipid values between the two groups ($p>0.05$). Although NLR and PLR were higher in the obese cases than in the controls, the difference was not statistically significant ($p>0.05$). SIII values were higher in both obese groups, and particularly in the MetS+ subjects, compared to the control group ($p=0.021$). Clinical and laboratory data for the MetS- and MetS+ obese subgroups and the healthy control group are shown in Table 1.

Evaluation of central, inner circle and outer circle macular thickness and volume measured using OCT revealed no significant difference between the sexes or between the two eyes ($p>0.05$). When the thickness and volume of the all macular retinal region was evaluated, no statistically significant difference was found between the groups (Tables 2 and 3).

Investigation of relations between clinical and laboratory variables and MRT and MRV revealed no significant relation between mean MRT and MRV and age, pubertal stage, BMI-SDS, WC-SDS, systolic/diastolic blood pressure, NLR, PLR or SIII in the control group. No significant difference was observed between age, pubertal stage, systolic/diastolic blood pressure, triglyceride, HDL cholesterol, or PLR in the MetS+ and MetS- obese groups ($p>0.05$). MRT and MRV values decreased significantly as BMI-SDS and WC-SDS increased in the obese groups ($p<0.05$). In contrast to the other groups, mean MRT ($r= -0.326$, $p=0.007$) and MRV ($r= -0.303$, $p=0.007$) values in the MetS+ obese group decreased significantly as HOMA-IR values increased. The decrease in MRT ($r= -0.544$, $p= 0.046$) and MRV ($r= -0.651$, $p=0.031$) in the MetS+ obese group was also negatively correlated with NLR. Mean MRT and MRV decreased as SIII increased in all obese subjects ($p<0.05$). The results of Pearson correlation analysis of MRT and MRV and clinical laboratory data are shown in Table 4.

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Discussion

Obesity and MetS associated with chronic inflammation can affect almost all systems in the body (1,2,20). This chronic inflammation also has the potential to produce changes in the retina and macular layer (20).

Previous studies have shown that obesity reduces the thickness of the retinal nerve fiber layer (RNFL) in children and affects choroid tissue (21-23).

Some studies have shown that obesity leads to changes in the macular layers in children. Although the methods and macular layers investigated differ in all these studies, it may nevertheless be concluded that obesity results in macular variability and damage in the pediatric age group (24-26). One study involving a MetS and impaired glucose tolerance model in rats demonstrated development retinal degeneration using microscopy and immunohistochemical methods (27).

To the best of our knowledge, ours is the first study to show macular changes in MetS+ children and the relations between that variability and metabolic and inflammatory parameters.

In the present study, mean MRT ($r = -0.457$, $p = 0.004$), and mean MRV ($r = -0.455$, $p = 0.004$) values in the obese group decreased as BMI-SDS increased. Negative correlation with BMI-SDS was determined only in the obese group. No correlation with BMI-SDS was observed in the control group ($p>0.05$). Mean MRT and MRV decreased as adipose tissue increased.

Increased adipose tissue in obese cases may cause chronic systemic inflammation and microvascular damage. Vascular endothelial damage, oxidative stress, and chronic inflammation can impair the permeability and supply of microvascular structures. Oxidative stress and hypoxia can develop in tissues. In additions, changes in leptin and adipokine levels, adipose tissue dysfunction, and insulin resistance can also develop. The production of inflammatory cytokines and reactive oxygen species (ROS) increases. Apoptosis and tissue necrosis are then triggered as a result. Studies have shown that oxidative stress may be an important factor in cell death (1,2, 28-30). Increased adipose tissue can affect MRT and MRV, and result in thinning. NLR, PLR and SIII, which can be simply and inexpensively calculated from complete blood count, have been shown to indicate subclinical inflammation in several previous studies (8,31-33). Furuncuoglu Y et al. (33) showed that NLR, PLR, and SIII are positively correlated with BMI in adults.

Another study of 26.016 adult patients determined positive correlation between NLR and MetS and obesity-related anthropometric data (32). One study of obese children with sleep apnea syndrome, a condition capable of leading to chronic hypoxia, showed that NLR and PLR increased together with obesity (34)**.**

No previous studies have investigated changes in NLR, PLR, and SIII in children with MetS. Ours is the first study to investigate NLR, PLR, and SIII in children and adolescents with the syndrome. Although these inflammatory markers were higher in all the obese cases in our study group than in the controls, the differences were not statistically significant ($p>0.05$). However, SIII values were higher in both obese groups, and particularly the MetS+ subjects, than in the control group ($p=0.021$). Ours is also the first study to investigate macular variability and metabolic parameters and inflammatory markers in children. In contrast to the other groups, mean MRT ($r= -0.326$, $p=0.007$) and MRV ($r=-0.303$,

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p=0.007) values decreased significantly as HOMA-IR values increased in the obese group with MetS. The decrease in mean MRT (r= -0.544, p= 0.046) and MRV (r= -0.651, p=0.031) in the MetS+ subjects was negatively correlated with NLR. Mean MRT and MRV also decreased as SIII increased in all our obese subjects ($p<0.05$).

There are a number of limitations to this study. Plasma levels of inflammatory mediators such as adiponectin, leptin, and IL-6 could not be measured. However, NLR, PLR and SIII values, proved to be markers of chronic subclinical inflammation in recent years, were investigated easily and inexpensively. In addition, due to the cross-sectional nature of our study, we were unable to determine whether weight loss and a decrease in adipose tissue would produce any change in MRT and MRV, particularly in obese children with MetS. Long-term, prospective observational studies in which weight control is established and inflammation reduced are now needed to show the effect on macular tissue of obesity and metabolic syndrome, and therefore of the chronic inflammatory process.

In conclusion, this study shows that mean MRT and MRV values decrease as BMI-SDS and WC-SDS increase in MetS+ obese children and adolescents. Mean MRT decreases as HOMA-IR values, a marker of insulin resistance, increases in children with MetS. Increased SIII and NLR may be a marker of chronic inflammation in MetS+ children and are associated with macular damage. Further long-term observational studies with larger participant numbers are now needed to confirm the results of this study.

Ethics

Ethics Committee Approval: The study was approved by the Tepecik Eğitim ve Araştırma Hastanesi Local Ethics Committee (Approval number: 2019/9-3)

Informed Consent: Consent form was filled out by all participants.

Authorship Contributions

Surgical and Medical Practices:
Concept: Hakan Öztürk, Bediz Özen,
Design: Hakan Öztürk , Bediz Özen, Gönül Çatlı
Data Collection or Processing: Bediz Özen, Hakan Öztürk, Gönül Çatlı
Analysis or Interpretation: Bediz Özen, Hakan Öztürk
Literature Search: Bediz Özen, Gönül Çatlı, Bumin Dündar
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References

1. Sabin MA, Kiess W. Childhood obesity: Current and novel approaches. Best Pract Res Clin Endocrinol Metab. 2015;29(3):327-338.
2. Lifshitz F. Obesity in children. J Clin Res Pediatr Endocrinol. 2008;1(2):53-60.
3. Galetta KM, Calabresi PA, Frohman EM, Balcer LJ. Optical coherence tomography (OCT): Imaging the visual pathway as a model for

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neurodegeneration. Neurother 2011;8:117-132.
4. Sánchez-Tocino H, Alvarez-Vidal A, Maldonado MJ, Moreno-Montañés J, García-Layana A. Retinal thickness study with optical coherence tomography in patients with diabetes. Invest Ophthalmol Vis Sci. 2002;43:1588-1594.
5. Srinivasan VJ, Wojtkowski M, Witkin AJ, Duker JS, Ko TH, Carvalho M, Schuman JS, Kowalczyk A, Fujimoto JG. High-definition and 3-dimensional imaging of macular pathologies with high-speed ultrahigh-resolution optical coherence tomography. Ophthalmology. 2006;113:2054-2065.
6. Forooghian F, Cukras C, Meyerle CB, Chew EY, Wong WT. Evaluation of time domain and spectral domain optical coherence tomography in the measurement of diabetic macular edema. Invest Ophthalmol Vis Sci. 2008;49:4290-4296.
7. Bird AC, Bok D. Why the macula? Eye (Lond). 2018; 32(5):858-862.
8. Faria SS, Fernandes PC Jr, Silva MJ, Lima VC, Fontes W, Freitas-Junior R, Eterovic AK, Forget P. The neutrophil-to-lymphocyte ratio: a narrative review. Ecancermedicalscience. 2016;12;10:702.
9. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio?. BMC Res Notes. 2017; 3;10(1):12.
10. Syauqy A, Hsu CY, Rau HH, Chao JC. Association of dietary patterns, anthropometric measurements, and metabolic parameters with C-reactive protein and neutrophil-to-lymphocyte ratio in middle-aged and older adults with metabolic syndrome in Taiwan: a cross-sectional study. Nutr J. 2018;19;17(1):106.
11. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity and stages of puberty. Arch Dis Child 1976;51:170-179.
12. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference Values for Weight, Height, Head Circumference and Body Mass Index in Turkish Children. J Clin Res Pediatr Endocrinol. 2015 ;7(4):280-293.
13. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006.
14. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, de Ferranti SD, Dionne JM, Falkner B, Flinn SK, Gidding SS, Goodwin C, Leu MG, Powers ME, Rea C, Samuels J, Simasek M, Thaker VV, Urbina EM. Subcommittee on screening and management of high blood pressure in children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140(3). pii: e20171904.
15. Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. Pediatrics 2005;114:500-503.
16. IDF consensus definition of metabolic syndrome in children and adolescents https://www.idf.org/e-library/consensus-statements/61-idf-

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consensus-definition-of-metabolic-syndrome-in-children-and-adolescents.
17. Hatipoglu N, Ozturk A, Mazicioglu MM, Kurtoglu S, Seyhan S, Lokoglu F. Waist circumference percentiles for 7- to 17-year-old Turkish children and adolescents. Eur J Pediatr. 2008;167(4):383-389.
18. Demir K, Özen S, Konakçı E, Aydın M, Darendeliler F. A Comprehensive Online Calculator for Pediatric Endocrinologists: ÇEDD Çözüm/TPEDS Metrics. J Clin Res Pediatr Endocrinol. 2017;9(2):182-184.
19. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology. 1991;98(Suppl):741-756.
20. Pacheco-Cervera J, Codoñer-Franch P, Simó-Jordá R, Pons-Vázquez S, Galbis-Estrada C, Pinazo-Durán MD. Reduced retinal nerve fibre layer thickness in children with severe obesity. Pediatric Obesity. 2015;10(6):448-453.
21. Özen B, Öztürk H, Çatlı G, Dündar B. An Assessment of Retinal Nerve Fiber Layer Thickness in Non-Diabetic Obese Children and Adolescents. J Clin Res Pediatr Endocrinol. 2018;10 (1):13-18.
22. Erşan I, Battal F, Aylanç H, Kara S, Arikan S, Tekin M, Gencer B, Tufan HA. Noninvasive assessment of the retina and the choroid using enhanced-depth imaging optical coherence tomography shows microvascular impairments in childhood obesity. Journal of AAPOS. 2016; 20:58-62.
23. Bulus AD, Can ME, Baytaroglu A, Can GD, Cakmak HB, Andiran N. Choroidal Thickness in Childhood Obesity. Ophthalmic Surg Lasers Imaging Retina. 2017;1;48(1):10-17.
24. Karti O, Nalbantoglu O, Abali S, Tunc S, Ozkan B. The assessment of peripapillary retinal nerve fiber layer and macular ganglion cell layer changes in obese children: a cross-sectional study using optical coherence tomography. Int Ophthalmol. 2017;37(4):1031-1038.
25. Demir S, Özer S, Alim S, Güneş A, Ortak H, Yılmaz R. Retinal nerve fiber layer and ganglion cell-inner plexiform layer thickness in children with obesity. Int J Ophthalmol. 2016;18;9(3):434-438.
26. Baran RT, Baran SO, Toraman NF, Filiz S, Demirbilek H. Evaluation of intraocular pressure and retinal nerve fiber layer, retinal ganglion cell, central macular thickness, and choroidal thickness using optical coherence tomography in obese children and healthy controls. Niger J Clin Pract. 2019;22(4):539-545.
27. Godisela KK, Reddy SS, Kumar CU, Saravanan N, Reddy PY, Jablonski MM, Ayyagari R, Reddy GB. Impact of obesity with impaired glucose tolerance on retinal degeneration in a rat model of metabolic syndrome. Mol Vis. 2017; 14;23:263-274.
28. Trayhurn P. Hypoxia and adipose tissue function and dysfunctionin obesity. Physiological Reviews, 2013;93(1):1-21.
29. Norouzirad R, González-Muniesa P, Ghasemi A. Hypoxia in Obesity and Diabetes: Potential Therapeutic Effects of Hyperoxia and Nitrate. Oxid Med Cell Longev. 2017;2017:5350267.
30. McMurray F, Patten DA, Harper ME. Reactive oxygen species and oxidative stress in obesity-recent findings and empirical

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approaches. Obesity. 2016;24(11):
2301-2310.
31. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio?. BMC Res Notes. 2017; 3;10(1):12.
32. Syauqy A, Hsu CY, Rau HH, Chao JC. Association of dietary patterns, anthropometric measurements, and metabolic parameters with C-reactive protein and neutrophil-to-lymphocyte ratio in middle-aged and older adults with metabolic syndrome in Taiwan: a cross-sectional study. Nutr J. 2018; 19;17(1):106.
33. Furuncuoğlu Y, Tulgar S, Dogan AN, Cakar S, Tulgar YK, Cakiroglu B. How obesity affects the neutrophil/lymphocyte and platelet/lymphocyte ratio, systemic immune-inflammatory index and platelet indices: a retrospective study. Eur Rev Med Pharmacol Sci. 2016;20(7):1300-1306.
34. Erdim I, Erdur O, Oghan F, Mete F, Celik M. Blood count values and ratios for predicting sleep apnea in obese children. Int J Pediatr Otorhinolaryngol. 2017;98:85-90.

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Table 1. Clinical and laboratory characteristics of the study groups.

Clinical or laboratory characteristics	**Control (n=48)**	**MetS(-)/obese (n=34)**	**MetS (+)/obese(n=28)**	***P***
Gender (Male/Female)	23/25	14/20	15/13	0.81
Age (years)	13.5[3.5	13.8[2.9	14.1 [3.3	0.99
Puberty stage (pre-pubertal/pubertal)	10 /38	8 /26	6/22	0.98
BMI SDS	0.5± 0.4	2.6± 0.8	3.1 [1.0	<0.0001
WC SDS	0.7 ± 0.9	2.2 ± 0.7	3.3 ± 1.4	<0.0001
Systolic BP (mmHg)	105.1 ±10.6	118.6± 10.1	128 [20.1	0.19
Diastolic BP (mmHg)	65.2 ±10.1	70.0 [12.3	79 [18.9	0.28
Fasting glucose(mg/dl)	81.7 ±8.7	86.7 ±8.9	89.1 ±10.5	0.65

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Fasting Insuline (mIU/ml)	8.3±3.1	19.6±9.8	26.7 ± 15.3	0.02
HOMA-IR	1.8 ±0.8	4.6±2.5	5.4 ± 3.1	0.01
Triglycerides (mg/dl)	132.3 ±60.8	137.9 ±82.3	149.9± 89.1	0.07
LDL-cholesterol (mg/dl)	92.3 ±28.9	99.3± 35.8	121.5 ±71.7	0.06
HDL-cholesterol (mg/dl)	46.6 ±10.7	42.2 ±10.9	36.9 ± 36.1	0.72
NLR	1.7	2.1	2.4	0.33
PLR	118.5	121.7	119.9	0.36
SIII	377.9	467.2	513.5	0.021

BMI SDS: Body mass index standart deviation score, BP: Blood pressure, HDL: High density lippprotein, HOMA-IR: Homeostasis model assesment of insülin resistance, Mets: Metabolic syndrome, NLR: Neutrophil/ lymphocyte ratio, PLR: Platelet/lymphocyte ratio, ,SIII: Systemic immun-inflammatory index, SDS: Standart deviation score, TG: Triglycerides WC:Waist circumference

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Macular Retinal Thickness	Control (n=40)	MetS(-)/obese (n=34)	MetS (+)/obese(n=28)	P
Central circle (µm)	271.5 ± 87.7	270.7 ± 101.9	265.5± 108.8	0.456
Inner circle (µm)				
Superior	356.5 ± 89.5	353.4 ± 90.8	350.7 ± 101.1	0.944
Temporal	343.7 ± 110.2	336.2 ± 113.0	335.2 ± 91.0	0.244
Inferior	352.5 ± 118.6	348.1 ± 135.8	339.2 ± 125.1	0.352
Nasal	354.4 ± 76.7	348.5 ± 108.3	340.5 ± 119.8	0.296
Outer circle (µm)				
Superior	305.3 ± 42.5	304.5 ± 79.3	299.4 ±81.3	0.092
Temporal	303.3 ± 96.3	303.1 ± 101.7	302.7 ±98.3	0.472
Inferior	299.7 ± 57.6	295.5 ± 80.8	292.8 ±87.5	0.398
Nasal	328.5 ± 78.1	325.6 ± 89.5	323.1 ±78.8	0.447

Table 2. Macular retinal thickness in control, MetS(-)/obese and MetS (+)/obese children.

MetS: Metabolic syndrome

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Table 3. Macular retinal volume in control and obese children with and without metabolic syndrome.

Macular Retinal Volume	**Control (n=48)**	**MetS(-)/obese (n=34)**	**MetS (+)/obese(n=28)**	**P**
Central circle (mm^3)	0.21± 0.69	0.21 ± 0.16	0.20 ± 0.19	0.433
Inner circle (mm^3)				
Superior	0.56 ± 0.14	0.55 ± 0.17	0.54 ± 0.21	0.960
Temporal	0.54 ± 0.17	0.53 ± 0.15	0.49 ± 0.19	0.261
Inferior	0.55 ± 0.18	0.55 ± 0.21	0.54 ± 0.29	0.413
Nasal	0.55 ± 0.11	0.55 ± 0.17	0.53 ± 0.18	0.325
Outer circle (mm^3)				
Superior	1.61 ± 0.22	1.59 ± 0.14	1.58 ±0.23	0.076
Temporal	1.60 ± 0.51	1.60 ± 0.53	1.57 ± 0.69	0.465
Inferior	1.68 ± 0.34	1.63 ± 1.62	1.67 ± 1.20	0.474
Nasal	1.74 ± 0.40	1.72 ± 0.47	1.70 ± 0.60	0.401

MetS: Metabolic syndrome

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Table 4. Correlation analysis of macular retinal thickness (MRT) and macular retinal volume (MRV)with the clinical and laboratory parameters in study groups.

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	RP	Age		Puberty stage		BMI SDS		WC SDS		Sistolic BP		Diastolic BP		HOMA-IR		TG		HDL		NLR		PLR		SIII	
		r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	P	r	p
Control (n=48)	MRT	0.020	0.901	0.051	0.752	-0.061	0.709	-0.151	0.079	0.071	0.662	0.082	0.616	-0.099	0.089	-0.077	0.832	0.036	0.870	-0.065	0.650	-0.069	0.821	-0.072	0.689
	MRV	0.019	0.909	0.078	0.631	-0.024	0.883	-0.259	0.091	0.054	0.742	0.060	0.712	-0.277	0.09	-0.069	0.642	0.045	0.779	-0.032	0.775	-0.023	0.820	-0.044	0.651
MetS (-) /obese (n=34)	MRT	-0.025	0.820	0.033	0.842	-0.457	0.004	-0.751	0.038	-0.090	0.593	-0.287	0.081	-0.047	0.781	0.039	0.819	-0.247	0.141	-0.232	0.093	-0.331	0.057	-0.391	0.048
	MRV	-0.041	0.807	0.023	0.893	-0.455	0.004	-0.459	0.047	-0.070	0.676	-0.274	0.096	-0.029	0.867	0.061	0.721	-0.237	0.158	-0.091	0.211	-0.301	0.061	-0.601	0.024
MetS (+) /obese (n=28)	MRT	0.027	0.934	0.067	0.773	-0.563	0.003	-0.511	0.033	-0.299	0.112	-0.321	0.098	-0.326	0.007	0.041	0.811	-0.222	0.221	-0.544	0.046	-0.298	0.088	-0.581	0.037
	MRV	0.033	0.765	0.056	0.892	-0.611	0.002	-0.477	0.038	-0.212	0.098	-0.378	0.087	-0.303	0.007	0.069	0.723	-0.245	0.156	-0.651	0.031	-0.288	0.095	-0.503	0.041

BMI SDS: Body mass index standart deviation score, BP: Blood pressure, HDL: High density lippprotein, HOMA-IR: Homeostasis model assesment of insülin resistance, Mets: Metabolic syndrome, MRT: Macular retinal thickness, MRV: Macular retinal volüme, NLR: Neutrophil/ lymphocyte ratio, PLR: Platelet/lymphocyte ratio, RP: Retinal parameters, SIII: Systemic immun-inflammatory index, SDS: Standart deviation score, TG: Triglycerides WC: Waist circumference

Uncorrected proof