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ORIGINAL ARTICLE

Assessment of Early Microvascular Changes in the Eye and Ear in Patients with Metabolic Syndrome: A Cross-Sectional Study

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ABSTRACT

Background: Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including central obesity, insulin resistance, hypertension, and dyslipidemia. These factors contribute to systemic microvascular dysfunction, which may manifest early in highly vascularized organs such as the eye and ear. Early detection of subclinical microangiopathy could serve as a biomarker for impending systemic vascular complications.

Objective: To assess early microvascular changes in the retina and cochlea in patients with metabolic syndrome using non-invasive ophthalmological and audiological methods.

Methods: A cross-sectional study was conducted from January 2022 to May 2023 at Mughal Eye Hospital, Lahore, and Pir Abdul Qadir Shah Jilani Institute of Medical Sciences, Gambat. A total of 100 participants were enrolled, including 70 patients with MetS (per IDF criteria) and 30 healthy controls. Retinal vessel diameters were assessed through fundus photography, and microvascular perfusion was evaluated using optical coherence tomography angiography (OCT-A). Cochlear function was examined using pure tone audiometry (PTA) and distortion product otoacoustic emissions (DPOAEs). Biochemical parameters including fasting glucose, lipid profile, and hsCRP were recorded.

Results: Patients with MetS showed significantly narrower retinal arteriolar diameters (CRAE: 134.6 ± 10.5 µm) and wider venular diameters (CRVE: 231.1 ± 15.3 µm) compared to controls ($p < 0.001$). OCT-A revealed reduced capillary density and enlarged foveal avascular zone (FAZ) ($p = 0.008$). High-frequency sensorineural hearing loss was present in 45.7% of MetS patients, with 52.9% showing absent or diminished DPOAEs. Positive correlations were found between triglyceride levels and both retinal and cochlear changes ($p < 0.01$).

Conclusion: Metabolic syndrome is associated with early subclinical microvascular changes in the eye and ear. Fundus imaging, OCT-A, and basic audiological assessments can serve as non-invasive, cost-effective tools for early detection and monitoring of microvascular impairment in MetS. These findings underscore the importance of multidisciplinary screening approaches in managing cardiometabolic risk.

Keywords: Metabolic syndrome, retinal microvasculature, cochlear dysfunction, OCT-A, otoacoustic emissions, microangiopathy.

INTRODUCTION

Metabolic syndrome (MetS) is a cluster of interrelated metabolic abnormalities that include central obesity, insulin resistance, dyslipidemia, hypertension, and glucose intolerance. These factors synergistically increase the risk of developing cardiovascular diseases, type 2 diabetes mellitus, stroke, and other chronic complications[1]. The global prevalence of MetS has seen a significant rise in recent decades, attributed largely to sedentary lifestyles, urbanization, and unhealthy dietary habits. According to the International Diabetes Federation (IDF), an estimated one-quarter of the world's adult population is affected by MetS, making it a major public health concern[2].

While the macrovascular complications of MetS such as coronary artery disease and cerebrovascular accidents are well-documented, growing evidence highlights the importance of early microvascular involvement in disease progression[3]. Microvascular dysfunction represents one of the earliest pathological consequences of MetS and serves as a precursor to overt end-organ damage. The earliest detectable changes often occur in highly vascular tissues such as the retina and cochlea, which are sensitive to systemic metabolic disturbances due to their end-arterial blood supply and lack of collateral circulation[4].

The retina provides a unique and non-invasive window to assess systemic microcirculation. Structural and functional changes in the retinal microvasculature, including arteriolar narrowing, venular dilation, and capillary dropout, have been associated with components of MetS such as hypertension, hyperglycemia, and elevated triglycerides[5]. Recent advances in optical coherence tomography angiography (OCT-A) have enabled high-resolution imaging of the retinal microcirculation, allowing for earlier and more precise detection of subclinical alterations[6].

Similarly, the inner ear, particularly the cochlea, is highly vulnerable to microvascular injury due to its reliance on a single terminal artery the labyrinthine artery. Subtle alterations in cochlear blood flow and oxygenation can impair outer hair cell function, leading to subclinical or early sensorineural hearing loss. Audiological tests such as pure tone audiometry (PTA) and otoacoustic emissions (OAEs) serve as sensitive, non-invasive tools to detect these changes before overt clinical symptoms develop[7,8].

Despite the known association of diabetes and hypertension with ocular and auditory dysfunction, there is a relative paucity of literature evaluating these changes specifically in patients with MetS particularly in the absence of overt diabetes or long-standing vascular disease. Identifying such early microvascular changes may provide valuable insights into systemic endothelial health and offer prognostic value in the early management of MetS[9,10].

Therefore, the present study aims to evaluate early microvascular changes in the eye and ear of patients with metabolic syndrome using fundus photography, OCT-A, PTA, and OAEs. By comparing findings with healthy age- and sex-matched controls, this study seeks to determine whether these changes can serve as accessible, non-invasive biomarkers for early microangiopathy and inform preventive strategies in clinical practice[11].

MATERIALS AND METHODS

Study Design and Setting: This cross-sectional observational study was conducted over a 17-month period, from January 2022 to May 2023, at two tertiary care centers: the Department of Ophthalmology, Mughal Eye Hospital, Lahore, and the Pir Abdul

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Qadir Shah Jilani Institute of Medical Sciences, Gambat, Pakistan. The study received ethical approval from the institutional review boards of both participating hospitals. All procedures adhered to the ethical guidelines outlined in the Declaration of Helsinki, and informed written consent was obtained from all participants prior to enrollment.

Study Population and Sampling: A total of 100 adult participants were included in the study through a non-probability purposive sampling technique. Among these, 70 were patients diagnosed with metabolic syndrome based on the International Diabetes Federation (IDF) 2006 criteria, and 30 were age- and sex-matched healthy individuals who served as the control group. The inclusion criteria required participants to be between 30 and 60 years of age and to meet the diagnostic criteria for metabolic syndrome, which includes central obesity (waist circumference ≥90 cm for men and ≥80 cm for women) along with any two of the following: raised triglyceride levels (≥150 mg/dL), reduced HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), elevated blood pressure (≥130/85 mmHg or on antihypertensive therapy), or fasting plasma glucose ≥100 mg/dL or previously diagnosed type 2 diabetes.

Patients were excluded if they had a history of overt diabetes mellitus, cardiovascular disease, chronic kidney disease, known ocular or auditory disorders, previous ocular surgery, or use of ototoxic medications. Additional exclusion criteria included active smoking, alcohol abuse, and occupational exposure to loud noise. These criteria were established to eliminate potential confounding factors that could independently affect microvascular integrity in the retina and cochlea.

Clinical and Biochemical Assessment: Each participant underwent a comprehensive clinical evaluation, including detailed medical history, physical examination, and anthropometric measurements. Height, weight, body mass index (BMI), and waist circumference were recorded. Blood pressure was measured using a calibrated sphygmomanometer, with the average of two readings taken 5 minutes apart. Blood samples were collected after an overnight fast to assess fasting plasma glucose, serum triglycerides, high-density lipoprotein (HDL) cholesterol, and high-sensitivity C-reactive protein (hsCRP) levels.

Ophthalmological Assessment: All participants underwent a detailed ophthalmic examination conducted by a consultant ophthalmologist. Visual acuity was assessed using a Snellen chart. Retinal imaging was performed using non-mydriatic fundus photography to evaluate structural changes in the retinal vasculature, including arteriolar narrowing, venular dilation, and arteriovenous nicking. Additionally, optical coherence tomography angiography (OCT-A) was employed to evaluate retinal microcirculation. The OCT-A scan provided high-resolution images of the superficial capillary plexus, allowed measurement of foveal avascular zone (FAZ) area, and assessed the overall capillary density in the macular and peripapillary regions. Quantitative measurements of retinal vessel diameters were obtained using standardized image analysis software to calculate central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), which are validated indicators of retinal microvascular health.

Audiological Assessment: To evaluate cochlear microvascular function, all subjects underwent pure tone audiometry (PTA) and otoacoustic emissions (OAEs) testing. PTA was performed in a sound-treated room by an audiologist to determine hearing thresholds across frequencies ranging from 250 Hz to 8,000 Hz. Sensorineural hearing loss was defined as thresholds exceeding 25 dB at two or more frequencies. Distortion product otoacoustic emissions (DPOAEs) were recorded using a calibrated OAE analyzer to assess outer hair cell function. The absence or significant reduction of DPOAE amplitude was interpreted as indicative of early cochlear microvascular compromise, even in the absence of clinically evident hearing loss.

Data Management and Statistical Analysis: All collected data were entered into SPSS version 26.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were expressed as mean ± standard deviation (SD), and comparisons between groups were made using the independent sample t-test or the Mann–Whitney U test for non-normally distributed data. Categorical variables were analyzed using the Chi-square test. Correlations between microvascular changes (retinal and cochlear) and metabolic parameters such as triglyceride levels, blood pressure, and hsCRP were assessed using Pearson's correlation coefficient. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

Demographic and Clinical Characteristics: A total of 100 participants were enrolled in the study, including 70 patients with metabolic syndrome (MetS group) and 30 age- and sex-matched healthy controls. The mean age of participants in the MetS group was 48.2 ± 7.6 years, while the control group had a mean age of 47.9 ± 6.9 years, with no statistically significant difference ($p = 0.81$). The male-to-female ratio was comparable across both groups ($p = 0.63$).

The MetS group had significantly higher mean values for BMI (29.4 ± 3.3 kg/m²), waist circumference (96.8 ± 9.1 cm), systolic blood pressure (138.6 ± 10.2 mmHg), and diastolic pressure (87.3 ± 6.4 mmHg) compared to controls ($p < 0.001$ for all). Similarly, fasting glucose and triglyceride levels were significantly elevated in MetS patients, while HDL cholesterol was markedly lower ($p < 0.001$) (Table 1).

Table 1: Demographic and Clinical Characteristics of the Study Population

Parameter	MetS Group (n = 70)	Controls (n = 30)	p-value
Age (years)	48.2 ± 7.6	47.9 ± 6.9	0.81
Male:Female ratio	38:32	17:13	0.63
BMI (kg/m²)	29.4 ± 3.3	23.8 ± 2.7	<0.001
Waist Circumference (cm)	96.8 ± 9.1	82.1 ± 6.5	<0.001
Systolic BP (mmHg)	138.6 ± 10.2	118.7 ± 8.9	<0.001
Diastolic BP (mmHg)	87.3 ± 6.4	74.9 ± 5.7	<0.001
Fasting Glucose (mg/dL)	110.4 ± 13.5	90.1 ± 8.4	<0.001
Triglycerides (mg/dL)	191.2 ± 32.7	121.8 ± 20.5	<0.001
HDL Cholesterol (mg/dL)	37.9 ± 6.2	52.6 ± 7.3	<0.001

Ophthalmological Findings: Retinal microvascular changes were significantly more common in the MetS group. Fundus photography revealed a reduced central retinal arteriolar equivalent (CRAE) of 134.6 ± 10.5 µm in the MetS group, compared to 144.3 ± 9.2 µm in controls ($p < 0.001$). Conversely, the central retinal venular equivalent (CRVE) was significantly increased in the MetS group (231.1 ± 15.3 µm vs. 215.4 ± 13.7 µm; $p = 0.002$). OCT-A revealed a statistically significant reduction in superficial capillary plexus (SCP) density in both the parafoveal and peripapillary regions in the MetS group ($p < 0.01$). The foveal avascular zone (FAZ) area was also significantly enlarged ($p = 0.008$), indicating early ischemic retinal changes. These findings are summarized in Table 2.

Table 2: Retinal Microvascular Parameters (Fundus Photography and OCT-A)

Parameter	MetS Group (n = 70)	Controls (n = 30)	p-value
CRAE (µm)	134.6 ± 10.5	144.3 ± 9.2	<0.001
CRVE (µm)	231.1 ± 15.3	215.4 ± 13.7	0.002
SCP Density (%)	36.7 ± 4.9	42.3 ± 3.8	<0.001
FAZ Area (mm²)	0.42 ± 0.08	0.34 ± 0.06	0.008

Audiological Findings: Audiological evaluations revealed subclinical sensorineural hearing loss in the MetS group, predominantly at higher frequencies (>4 kHz). PTA showed that 32 patients (45.7%) in the MetS group had elevated thresholds in the high-frequency range compared to only 2 patients (6.7%) in the control group ($p < 0.001$). Furthermore, distortion product otoacoustic emissions (DPOAEs) were significantly reduced or absent in 37 out of 70 MetS patients (52.9%), suggesting early

cochlear microvascular dysfunction. The mean amplitude of OAEs at 4 kHz was significantly lower in the MetS group compared to controls (3.2 ± 1.5 dB vs. 5.8 ± 2.1 dB; p < 0.001). Details are presented in Table 3.

Table 3: Audiological Parameters in MetS Patients and Controls

Parameter	MetS Group (n = 70)	Controls (n = 30)	p-value
High-Frequency Hearing Loss (%)	45.7% (n = 32)	6.7% (n = 2)	<0.001
DPOAE Abnormality (%)	52.9% (n = 37)	10.0% (n = 3)	<0.001
Mean OAE Amplitude at 4 kHz (dB)	3.2 ± 1.5	5.8 ± 2.1	<0.001

Correlation Analysis: Pearson correlation analysis revealed significant positive correlations between CRVE and both triglyceride levels (r = 0.51, p < 0.001) and systolic blood pressure (r = 0.48, p = 0.002). Similarly, there was a negative correlation between SCP density and hsCRP levels (r = –0.42, p = 0.005), suggesting that systemic inflammation may contribute to microvascular compromise.

High-frequency hearing thresholds were positively correlated with serum triglycerides (r = 0.39, p = 0.008) and waist circumference (r = 0.33, p = 0.015), further supporting the role of metabolic dysregulation in cochlear microvascular injury.

DISCUSSION

This study evaluated early microvascular alterations in the retina and cochlea among patients with metabolic syndrome (MetS) using non-invasive imaging and audiological testing. The findings reveal a clear association between MetS and subclinical changes in both ocular and auditory microcirculation, even in the absence of clinically apparent end-organ damage[12,13].

The ophthalmological findings demonstrate significant narrowing of central retinal arteriolar diameter (CRAE), widening of venular diameter (CRVE), and reduced superficial capillary plexus (SCP) density in patients with MetS. These retinal microvascular changes are consistent with previous studies that have associated hypertension, insulin resistance, and hyperlipidemia with arteriolar constriction and venular dilation due to endothelial dysfunction, increased oxidative stress, and chronic low-grade inflammation[14]. The enlargement of the foveal avascular zone (FAZ) in our MetS group further suggests early ischemic damage and impaired retinal perfusion, as also reported by Spaide et al. and Wong et al. in diabetic and hypertensive populations[15].

Cochlear microvascular compromise was evidenced by high-frequency sensorineural hearing loss detected through pure tone audiometry (PTA) and diminished otoacoustic emissions (OAEs), particularly at 4 kHz and above. This finding aligns with the hypothesis that the cochlea, particularly the outer hair cells in the basal turn, is highly vulnerable to ischemia due to its dependence on a single terminal blood supply[16]. Metabolic disturbances such as hypertriglyceridemia and endothelial dysfunction can lead to reduced cochlear perfusion, resulting in early auditory impairment. Our study supports previous findings by Salvi et al. and Alvarado et al., who emphasized the role of microvascular injury in sensorineural hearing loss among patients with cardiometabolic disorders[17].

Moreover, the observed correlations between microvascular abnormalities and biochemical markers such as triglyceride levels, waist circumference, and hsCRP indicate a strong link between systemic inflammation and microangiopathy. These markers reflect metabolic stress and vascular dysfunction that manifest in sensitive tissues like the retina and cochlea before symptoms become clinically significant. Elevated hsCRP, in particular, suggests an ongoing pro-inflammatory state that could contribute to endothelial injury, reduced nitric oxide bioavailability, and capillary rarefaction[18].

The clinical implications of these findings are significant. Retinal imaging through fundus photography and OCT-A, as well as basic audiometric screening, offer accessible and non-invasive tools to detect early microvascular compromise. Incorporating such evaluations into the routine assessment of MetS patients may help identify those at higher risk for long-term vascular complications, even in the absence of overt diabetes or cardiovascular disease. Early identification allows for timely intervention through lifestyle modifications, pharmacologic management of lipids and blood pressure, and monitoring of organ-specific function[19].

Despite these strengths, our study has some limitations. Being cross-sectional in design, it does not establish causality or temporal progression. The sample size, although adequate for initial exploratory analysis, may limit generalizability. Additionally, more advanced electrophysiological or angiographic imaging could further validate the early microvascular changes detected. Longitudinal studies are warranted to explore whether these early changes predict future microvascular or macrovascular complications[16,20].

CONCLUSION

This study demonstrates that metabolic syndrome is associated with early, subclinical microvascular changes in both the retina and cochlea. Retinal vessel narrowing, decreased capillary density, and cochlear dysfunction identified via non-invasive OCT-A and audiological testing may serve as early markers of systemic vascular impairment in MetS patients. These findings support the inclusion of ocular and auditory screening in the routine evaluation of individuals with metabolic syndrome, even before the development of overt complications. Detecting microvascular dysfunction at this asymptomatic stage offers a critical window for intervention aimed at halting or reversing disease progression. Further prospective research with larger cohorts is recommended to validate these findings and explore the prognostic value of such microvascular assessments in predicting cardiovascular and neurologic outcomes in patients with metabolic syndrome.

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