

## Metabolic Syndrome is Associated with Increased Severity of Diabetic Retinopathy

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### Abstract

**Purpose:** To study the association of metabolic syndrome with severity of diabetic retinopathy.

**Materials and method:** Seventy-one consecutive cases of type 2 diabetes mellitus of more than 10 years duration aged 38 to 82 years were included. Metabolic syndrome was identified as per American Heart Association-National Cholesterol Education Programme Adult Treatment Panel III (AHA-NCEP ATP III) criteria. All the cases were assessed for log MAR visual acuity, intraocular pressure (IOP) and seven field fundus photography. The photographs were scored for 16 diabetic lesions. A single severity level (identical to the ETDRS Interim Scale) was calculated for each eye by using the Vanderbilt Classification System. Data was analysed using paired t-test.

**Results:** Of the 71 cases, 47 cases fulfilled at least 3 of the ATP III criteria for metabolic syndrome. Among the cases of metabolic syndrome, 18 cases fulfilled 3 criteria, 28 cases fulfilled 4 criteria and 1 case fulfilled all the 5 criteria. The analyses of the mean Vanderbilt score for severity of retinopathy showed significantly higher score (more severe retinopathy) in cases of metabolic syndrome ( $p < 0.001$ ). Higher IOP was observed in cases of metabolic syndrome ( $p < 0.001$ ). LogMAR visual acuity deteriorated ( $p < 0.01$ ), severity of retinopathy and intraocular pressure increased ( $p < 0.001$ ,  $p < 0.001$ , respectively) with an increase in the number of components of metabolic syndrome. Triglyceride levels showed positive correlation with severity of retinopathy ( $p < 0.001$ ) and IOP ( $p < 0.001$ ). High density lipoprotein (HDL) levels also showed positive correlation with vision ( $p < 0.001$ ), severity of retinopathy ( $p < 0.001$ ) and IOP ( $p < 0.001$ ).

**Conclusion:** Metabolic syndrome is significantly associated with increased severity of diabetic retinopathy, decreased visual acuity and increased IOP.

**Keywords:** Metabolic syndrome; Diabetes mellitus; Diabetic retinopathy; Intraocular pressure

### Introduction

Metabolic syndrome has become increasingly common in the developed world and now even in the developing countries. It is known under various other names, such as Syndrome X, insulin resistance syndrome, Reaven's syndrome or CHAOS (Coronary artery disease, Hypertension, Atherosclerosis, Obesity, and Stroke) and Deadly quartet [1-3].

It has been estimated that about 20–25 percent of US adults are affected by metabolic syndrome [4,5]. However, the prevalence of metabolic syndrome in people with type 2 diabetes mellitus in Central India was found to be 45.8 percent as per Adult Treatment Panel-III criteria [6].

American Heart Association (AHA) modified Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) criteria is the most current and widely used one [7]. More over in this definition, presence of type 2 diabetes does not exclude a diagnosis of metabolic syndrome.

According to the AHA-NCEP ATP III criteria, the metabolic syndrome is identified by the presence of three or more of the following components: Elevated waist circumference, elevated triglycerides, reduced High density lipoprotein (HDL) cholesterol, elevated blood pressure and elevated fasting glucose.

In this definition, treatment for diabetes or hypertension forms one of the criteria unlike in other definitions which use blood glucose value (fasting or glucose tolerance test values) or blood pressure as one of the criteria. Diabetic cases with metabolic syndrome are at high risk for developing various diseases primarily coronary artery disease [8,9]. Type 2 diabetes mellitus individuals with metabolic syndrome seemingly are also susceptible to polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer [9-13].

It is not yet known whether type 2 diabetes individuals with metabolic syndrome are at a high risk for ocular changes when compared with type 2 diabetes individuals without metabolic syndrome. Hence, a tertiary care center-based study was undertaken to evaluate the association of change in visual acuity, intraocular pressure (IOP) and severity of retinopathy by using the Vanderbilt Classification System [14] in metabolic syndrome.

## Material and Methods

Our study had institutional review board clearance and was performed in accordance to the tenets of the Helsinki declaration. Seventy-one consecutive cases of type 2 diabetic mellitus with more than 10 years duration, aged 38 to 82 years, attending diabetes and retina clinic of our tertiary care centre were included. Exclusion criteria included cases having media haze (corneal, lenticular, and vitreous), which was hampering complete retina evaluation. Patients who had undergone laser or surgery for glaucoma, retinopathy or retinal detachment were excluded. Patients already on treatment for dry eye or glaucoma or with pre-existent ocular illness like Stevens Johnson syndrome and other retinal vascular disorders were also excluded. Patients who were not willing or with poor general condition were not enrolled.

The duration of illness was defined as the duration from the time of the diagnosis of diabetes mellitus given by the participant until the time of the examination. Current age was defined as the age at the time of the examination.

The examination consisted of an explanation of the study, measurement of the blood pressure, refraction and assessment of the logMAR best corrected visual acuity (LogMAR is expressed as decadic logarithm of minimum angle of resolution with 20/20 line equivalent to LogMAR 0.00 and the 20/200 line to LogMAR 1.0) and slit-lamp biomicroscopy of the anterior segment. Measurement of the intraocular pressure using applanation tonometry was done. Cases having intraocular pressure (IOP) greater than 21 mm of Hg or showing optic disc changes were subjected to automated perimetry using Humphrey's automated visual field analyzer (Carl Zeiss Humphrey Field Analyser 750i, Dublin, CA, USA). Gonioscopic evaluation of the angle of anterior chamber was done using Goldmann three mirror lens. Fundus examination was done by slit lamp biomicroscopy with a 90-diopter lens and indirect ophthalmoscopy. Seven field fundus photography was done in all cases using Zeiss fundus camera FF 450 Plus with pixel width of 0.0054 and image size 2588 x 1958. Cases showing retinal changes were subjected to fundus fluorescein angiography.

The seven field fundus photographs were scored for retinopathy. The photographs were scored for 16 diabetic lesions. A single severity level (identical to the ETDRS Interim Scale) was calculated for each eye by using, the Vanderbilt Classification System (Table 1) [14]. This method has been proven to give quantitative data (numeric values) and evaluate incremental changes in an accurate, reproducible manner and is highly reliable between graders. The person scoring the photographs did not know the history or reports of the investigations of the case while scoring the photographs for severity to avoid bias. This scoring system gave a retinopathy score from 10 to 75, higher scores indicating more severity.

	Ma and all other lesions absent
14	HE, SE, or IRMA definite, Ma absent
15	RH definite, Ma absent
20	Ma definite, no other lesions present
30	Ma plus SE, IRMA, or VB questionable; Ret.Hem. present, H/Ma < 5/1*; or HE definite Levels 41 and above require Ma s: 3/1
41	IRMA a 3/1-3; or SE a 3/1-3
45	IRMA 2= 3/4-5; or SE s 3/4-5; or VB definite; or H/Ma a 5/1-3
51	H/Ma a 5/4-5; or VB > definite/2-3; or Combination of SE a 4/4-5, IRMA a 3/2-3, and H/Ma > 5/1
55	IRMA a= 4/2-3; or VB a def/2-3, plus 2 other P2 lesions; or 4 P2 lesions; or H/Ma a 5/4-5 plus 2 other P2 lesions
61	FPE, or FPD definite, NVE or NVD absent; or NVE definite
65	Either NVE s 4/1; or NVD a 3/1; or VH or PRH a 3/1, plus NVE > 3/1
71	VH or PRH > 4/1; or NVE a 4/1, and VH or PRH a 3/1; or NVD a 3/1, and VH or PRH > 3/1; or NVD a 4/1
75	NVD > 4/1, and VH or PRH a 3/1

**Table 1:** Vanderbilt classification system for scoring of diabetic retinopathy lesions, Ma=Micro Aneurysms; HE=Hard Exudates; SE=Soft Exudates; IRMA=Intraretinal Micro Vascular Abnormalities; RH=Retinal Hemorrhage; VB=Venous Beading; FPE=Fibrous Proliferation Elsewhere; FPD=Fibrous Proliferation on Disc; NVE=Neovascularization Elsewhere; NVD=Neovascularization on Disc; VH=Vitreous Hemorrhage; PRH=Preretinal Hemorrhage.

Numbers indicate summary scores of maximum grade/number of fields with maximum.

P2 lesions=SE  $\geq$  3/2-3;

IRMA  $\geq$  3/2-3; VB  $\geq$  3/2-3; H/Ma  $\geq$  5/1.

Clinically significant macular edema (CSME) global grading scores were: 1=no evidence; 2=questionable; 3=definitely present. (For this study, the definition of CSME, as defined by the ETDRS was used). CSME scores were added to the score thus obtained and final score obtained.

Fasting and post prandial blood glucose, serum levels of high density lipoprotein (HDL), triglycerides and glycosylated hemoglobin was estimated as per standard protocol.

Statistical significance of mean values was assessed using two-sample t test. By linear regression analysis best corrected visual acuity, severity of retinopathy and IOP were compared with the number of components of metabolic syndrome, triglyceride levels and HDL level.

## Results

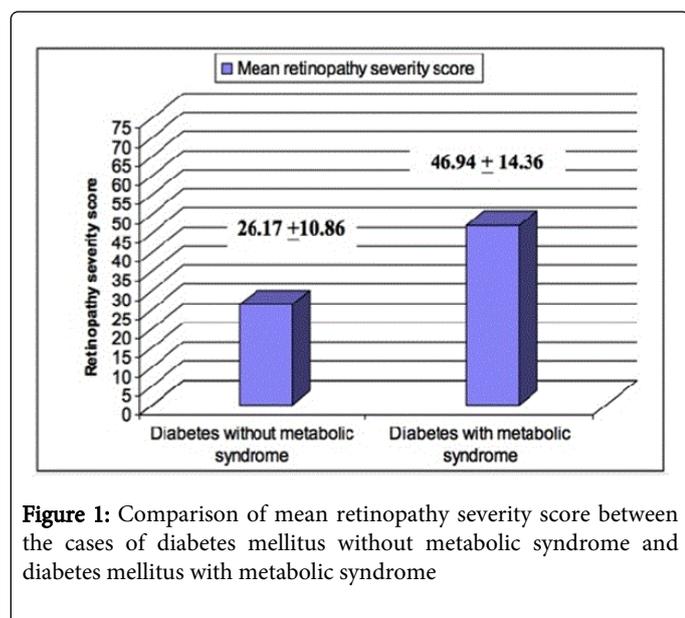
A total of 141 eyes were evaluated in the study. One eye with phthisis bulbi was excluded. Of the 71 cases, 47 cases fulfilled at least 3 of the ATP III criteria for metabolic syndrome. Among the cases of metabolic syndrome, 18 cases fulfilled 3 criteria, 28 cases fulfilled 4 criteria and 1 case fulfilled all the 5 criteria's.

The mean age of the cases included in the study was 53.54±12.41 years in cases of diabetes without metabolic syndrome. Among the cases of diabetes with metabolic syndrome, mean age of the cases was 55.91±9.91 years. No statistically significant difference in the ages of cases in the two groups was observed (p=0.22).

Among the cases of diabetes with metabolic syndrome, 27 were men and 20 were women. In cases of diabetes without metabolic syndrome, 17 were men and 7 were women. No statistically significant difference in the gender distribution of cases in the two groups was observed (χ<sup>2</sup>=0.71, p=0.40).

The mean duration of diabetes in patients of diabetes without metabolic syndrome was 13.43±2.31 years and with metabolic syndrome was 12.26±2.32 years. A statistically significant difference was observed (p=0.52).

Mean Vanderbilt score for severity of retinopathy was 26.17±10.86 for cases of diabetes without metabolic syndrome. For the metabolic syndrome cases, the mean score was 46.94±14.36 (Figure 1). A statistically significant difference was observed (t=8.81, p<0.001).



**Figure 1:** Comparison of mean retinopathy severity score between the cases of diabetes mellitus without metabolic syndrome and diabetes mellitus with metabolic syndrome

Mean IOP (in mm Hg) of the diabetes cases without metabolic syndrome was 14.20±2.20 mm Hg and in diabetes cases with metabolic syndrome, it was 18.44±5.10 mm Hg. A statistically significant difference was observed (t=6.47, p<0.001).

The cases were subdivided into 4 groups according to the number of components of metabolic syndrome present. The first group had diabetes only while the subsequent groups had additional 1, 2 or 3 components with diabetes being the common factor. There was a linear increase in the fall in visual acuity, severity of retinopathy and intraocular pressure with increase in number of components of metabolic syndrome. It was observed that the visual acuity deteriorated with an increase in the number of components of metabolic syndrome (p<0.01). It was seen that the severity of retinopathy (p<0.001) and IOP (p<0.001) increased with increase in number of components of metabolic syndrome (Table 2).

No. of components	No. of eyes	Best corrected visual acuity (mean value)	Mean Retinopathy score	Mean intraocular pressure
Diabetes only	24	-0.33 ± 0.31	23.52 ± 11.09	13.26 ± 1.86
Diabetes+1 component*	24	-0.35 ± 0.37	28.71 ± 10.23	13.58 ± 2.70
Diabetes+2 components*	36	-0.69 ± 0.59	42.20 ± 14.76	15.26 ± 4.20
Diabetes+3 components*	56	-0.81 ± 0.74	50.20 ± 13.55	20.34 ± 4.25

**Table 2:** Correlation of number of components of metabolic syndrome with vision, retinopathy score and intraocular pressure of metabolic syndrome

The change was not very significant if the number of components of metabolic syndrome varied by only 1 component. If the number of components of metabolic syndrome varied by more than 1 component, the groups had a significant change in best corrected visual acuity, mean retinopathy score and mean IOP (Table 3).

§	Best corrected visual acuity		Retinopathy score		Intraocular pressure	
	t	P	t	P	t	P
Diabetes only Vs Diabetes+1 component*	0.2	0.8	1.69	0.1	0.4	0.7
Diabetes only Vs Diabetes+2 components*	2.74	<0.01	5.28	<0.001	2.19	<0.05
Diabetes only Vs Diabetes+3 components*	3.06	<0.01	8.49	<0.001	7.82	<0.001
Diabetes+1 component* Vs Diabetes+2 components*	2.51	<0.05	3.89	<0.001	1.73	0.1
Diabetes+1 component* Vs Diabetes+3 components*	2.88	<0.01	6.95	<0.001	7.18	<0.001
Diabetes+2 component* Vs Diabetes+3 components*	0.82	0.4	2.67	<0.01	5.62	<0.001

**Table 3:** Linear regression analysis among best corrected visual acuity, retinopathy score and intraocular syndrome of metabolic syndrome

Triglyceride level showed strong correlation with severity of retinopathy (p<0.001) (Figure 2) and IOP (p<0.001). HDL showed positive correlation with vision (the higher the HDL the better the vision) but negative correlation with severity of retinopathy (Figure 3) and IOP (the higher HDL, the less severe diabetic retinopathy and less severe increase in the IOP).

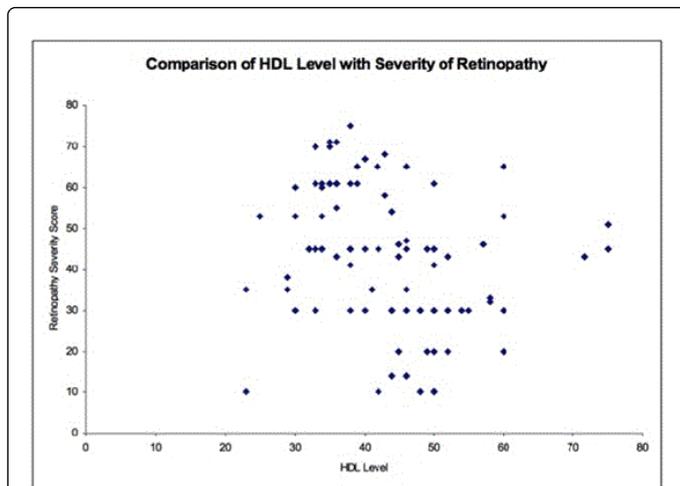


Figure 2: Comparison of HDL levels with severity of retinopathy

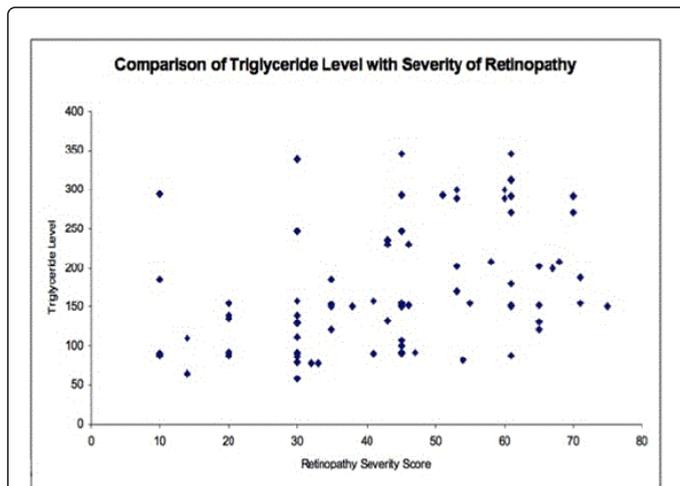


Figure 3: Comparison of triglyceride Level with severity of retinopathy

## Discussion

Increased severity of retinopathy was observed with increasing components of metabolic syndrome. Previous study by Corrêa et al. [15] found that the severity of diabetic retinopathy appeared to be associated with risk factors such as duration of disease. In our study, no statistically significant difference in duration of disease was found in the two groups.

When the ocular parameters such as best corrected visual acuity, retinopathy severity score and intraocular pressure were compared in the cases, significantly worse visual status and significantly higher score (more severe retinopathy) in diabetes cases with metabolic syndrome was found. A previous study done by Malik et al. [16] had showed that retinopathy lesions similar to diabetic retinopathy can be seen in cases of metabolic syndrome even if they were not suffering from diabetes signifying that there retinopathy lesions may be caused by other components of metabolic syndrome. This could probably

explain the higher mean Vanderbilt scores for severity of retinopathy among cases of diabetes with metabolic syndrome.

Significantly higher intraocular pressure in eyes of diabetes cases with metabolic syndrome was found. This correlated with findings of Oh et al. [17] who also found that intraocular pressure was higher in participants with metabolic syndrome, as compared to those who did not have metabolic syndrome.

It was observed that the visual acuity deteriorated whereas severity of retinopathy and intraocular pressure increased with an increase in the number of components of metabolic syndrome. If the number of components varied by more than 1 component, the groups had a significant change in best corrected visual acuity, mean retinopathy score and mean intraocular pressure.

Our findings correlated with the findings of Oh et al. [17] who also found that the mean intraocular pressure tends to increase linearly with the presence of increasing numbers of components for metabolic syndrome.

Searches for previous studies correlating number of components of metabolic syndrome with mean retinopathy severity score and mean intraocular pressure have not yielded any result.

## Conclusions

Cases of diabetes mellitus with metabolic syndrome have significantly poor visual acuity, increased severity of retinopathy and higher IOP than cases of diabetes mellitus who do not have metabolic syndrome. Also, it was observed that as the number of components increased by more than 1 component, the groups showed significant change in the above mentioned parameters.

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