

# Evaluation of the Severity of Diabetic Retinopathy in Correlation with the Severity of Coronary Heart Disease in Diabetic Patients: A Coronary Angiographic Study

Amira Nowara <sup>1\*</sup>, Mohamed Yakoot <sup>1</sup>, Ahmed Soliman <sup>2</sup>, Mohamad Gad <sup>3</sup>, Mohamad Al-Adlany <sup>1</sup>

<sup>1</sup> Internal medicine Department, Faculty of Medicine - Mansoura University

<sup>2</sup> Cardiology Department, Faculty of Medicine - Mansoura University

<sup>3</sup> Ophthalmology Department, Faculty of Medicine - Mansoura University

\*Corresponding Author: Amira Nowara, Internal medicine Department, Faculty of Medicine - Mansoura University, Egypt.

Received Date: 14 December 2020 | Accepted Date: 22 December 2020 | Published Date: 30 December 2020

**Citation:** Amira Nowara, Mohamed Yakoot, Ahmed Soliman, Mohamad Gad, Mohamad Al-Adlany, (2020), Evaluation of the Severity of Diabetic Retinopathy in Correlation with the Severity of Coronary Heart Disease in Diabetic Patients: A Coronary Angiographic Study, *J. Endocrinology and Disorders*, 4(2): DOI: [10.31579/2640-1045/224](https://doi.org/10.31579/2640-1045/224)

**Copyright:** © 2020, Amira Nowara. This is an open-access article distributed under the terms of The Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## Abstract

**Background:** Diabetes mellitus (DM) is a global health problem characterized by chronic hyperglycemia leading to both microvascular and macrovascular complications. Among these, diabetic retinopathy (DR) is a major cause of visual loss, while coronary heart disease (CHD) is a leading cause of mortality in diabetic patients. Previous studies have suggested that DR, as a microvascular manifestation, may reflect systemic vascular pathology, linking retinal microangiopathy with coronary atherosclerosis.

**Objective:** To assess the relationship between the severity of diabetic retinopathy and the severity of coronary heart disease in diabetic patients using coronary angiography.

**Methods:** This cross-sectional study included 99 diabetic patients (53 males, 46 females; aged 20–70 years) with suspected coronary artery disease who underwent elective coronary angiography at Mansoura Specialized Medical Hospital. Each participant underwent clinical evaluation, laboratory tests (FBG, HbA1c, lipid profile, renal and liver function), ECG, echocardiography, and detailed fundus examination using direct and indirect ophthalmoscopy as well as fluorescein angiography. Severity of CHD was assessed by Gensini and vessel scores, while DR was classified by Early Treatment Diabetic Retinopathy Study (ETDRS) and Scottish grading systems.

**Results:** A statistically significant association was observed between the number of occluded coronary vessels and DR grade, while the correlation between DR grade and Gensini score was not significant. Multivariable regression analysis identified DR presence (irrespective of grade) as an independent predictor of severe coronary stenosis ( $\geq 70\%$ ), with patients exhibiting DR having 2.8-fold higher odds of significant coronary lesions.

**Conclusions:** The study concludes that diabetic retinopathy is strongly associated with increased risk and severity of coronary heart disease, independent of traditional cardiovascular risk factors. Thus, fundus examination may serve as a simple, non-invasive tool for early identification of patients at risk for CHD.

**Key Words:** diabetic retinopathy; coronary heart disease; type 2 diabetes mellitus; gensini score; angiography; vascular complications

## Introduction

Diabetes mellitus (DM) is one of the most challenging public health issues of the 21st century, affecting millions worldwide and showing an alarming rise in prevalence. The disease is characterized by chronic hyperglycemia due to impaired insulin secretion, insulin resistance, or both, resulting in progressive vascular complications. These complications are broadly classified into microvascular complications—such as retinopathy, nephropathy, and neuropathy—and macrovascular

complications—such as coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease. Among them, diabetic retinopathy (DR) remains a leading cause of blindness among working-age adults, while CHD stands as a primary cause of death among diabetic patients (Attia et al., 2020).

The coexistence of these two complications highlights the possibility of shared pathogenic mechanisms. Both DR and CHD are consequences of endothelial dysfunction, chronic inflammation, oxidative stress, and the accumulation of advanced glycation end-products (AGEs). Previous epidemiological studies, including the Framingham Heart and Eye Study, have suggested that the microvascular changes seen in the retina may reflect systemic vascular dysfunction, implying that retinal microangiopathy could serve as a marker for coronary atherosclerosis (Um et al., 2016). However, despite this theoretical link, the exact correlation between DR severity and coronary artery disease burden remains incompletely understood, especially when quantified using coronary angiographic scoring systems (Jibran et al., 2018).

Existing research on the relationship between diabetic retinopathy and coronary heart disease has yielded inconsistent findings. Some studies have demonstrated a significant association between the presence or severity of DR and increased CHD risk, while others reported weak or no correlation when controlling for traditional cardiovascular risk factors such as hypertension, dyslipidemia, and obesity (Habib et al., 2019). Furthermore, many earlier studies relied on non-invasive diagnostic methods like electrocardiography or stress testing, which may not accurately reflect the true extent of coronary atherosclerosis. Limited studies have used coronary angiography—considered the gold standard—to objectively quantify coronary artery involvement in relation to DR severity, particularly in Egyptian or Middle Eastern populations (Tavares et al., 2016).

This study addresses this research gap by directly assessing the correlation between the severity of diabetic retinopathy and the angiographically determined severity of coronary heart disease using validated scoring systems such as the Gensini and vessel scores. The novelty lies in combining ophthalmologic and coronary angiographic data to evaluate whether retinal microvascular changes can serve as a surrogate marker for systemic macrovascular disease. Such correlation, if proven, could have important clinical implications—enabling ophthalmologists to identify high-risk patients for CHD through simple fundus examinations, and guiding physicians toward early cardiological assessment in diabetic patients with advanced DR (Cheng et al., 2018).

The present study aims to evaluate the degree and severity of diabetic retinopathy in correlation with the degree and severity of coronary heart disease in diabetic patients using coronary angiography. The ultimate goal is to determine whether the severity of DR could serve as a non-invasive predictor of coronary atherosclerosis, thereby facilitating early detection and risk stratification of cardiovascular disease among diabetic individuals.

## Patients And Methods

After approval from the Institutional Ethical Committee and obtaining informed written consent from all participants, this cross-sectional study was conducted on a total of 124 diabetic patients, including both male and female participants diagnosed with type 2 diabetes mellitus (T2DM) at the Specialized Medical Hospital and Ophthalmic Center, Faculty of Medicine, Mansoura University, between July 2017 and March 2019. After excluding 25 patients due to incomplete data or loss to follow-up, the final study sample consisted of 99 patients aged between 20–70 years. All participants were known diabetic patients admitted for coronary angiography due to ischemic symptoms or positive non-invasive cardiac tests.

## Inclusion and Exclusion Criteria:

### *Inclusion criteria comprised:*

1. Patients with type 1 or type 2 diabetes mellitus.
2. Ischemic patients with atherosclerotic coronary artery disease admitted for coronary angiography.

3. Age between 20 and 70 years.

### *Exclusion criteria included:*

1. Patients aged <20 or >70 years.
2. History of cerebrovascular stroke or malignancy.
3. Presence of chronic hepatic or renal disease or other non-atherosclerotic cardiovascular diseases.

## Study Procedures:

### *History Taking*

A detailed medical history was recorded for each participant, including demographic data (age, sex, occupation), diabetes duration and type, treatment modality (insulin or oral drugs), glycemic control, history of smoking, other diabetic complications, previous cardiovascular events, and ocular disorders such as glaucoma or cataract.

### *Clinical Examination*

Comprehensive general and systemic examinations were performed. This included vital signs, blood pressure, cardiovascular and abdominal examination, and detailed ophthalmologic evaluation using direct and indirect ophthalmoscopy with +90D or 3-mirror lenses. Anthropometric measurements—such as BMI and waist circumference—were used to assess obesity. Additionally, metabolic syndrome was identified using both IDF and AHA/NHLBI criteria.

### *Investigations*

#### **1. Laboratory Investigations:**

- Fasting plasma glucose (FPG) and 2-hour postprandial plasma glucose (2hPPG).
- Glycated hemoglobin (HbA1c) to assess long-term glycemic control.
- Lipid profile: total cholesterol (TC), triglycerides (TGs), high-density lipoprotein (HDL), and low-density lipoprotein (LDL).
- Renal function tests: serum creatinine.
- Liver function tests: ALT, AST, INR, serum albumin, and bilirubin.

#### **2. Cardiac Investigations:**

- Electrocardiography (ECG): 12-lead ECG to detect ischemic changes or previous infarction.
- Echocardiography: used to assess left ventricular function, ejection fraction, and to exclude cardiomyopathies.
- Coronary angiography: performed via the femoral approach using a Siemens Axiom Artis Cath/Angio System. The Left Anterior Descending (LAD) and Left Circumflex (LCX) arteries were visualized in at least 4 projections, and the Right Coronary Artery (RCA) in at least 2 projections.

#### **Assessment of Coronary Artery Disease:**

Two scoring systems were used:

a) **Vessel Score:** based on the number of major vessels with  $\geq 50\%$  luminal narrowing.

- Score 0 = No vessel involvement
- Score 1 = Single-vessel disease
- Score 2 = Double-vessel disease
- Score 3 = Triple-vessel disease

Left main stenosis was considered as single-vessel disease.

b) **Gensini Score:** each lesion was assigned a score according to the degree of luminal narrowing:

- 25% = 1 point
- 50% = 2 points
- 75% = 4 points
- 90% = 8 points
- 99% = 16 points
- 100% (total occlusion) = 32 points

Each lesion's score was then multiplied by a factor representing the anatomical importance of the lesion site (e.g., left main =  $\times 5$ , proximal LAD =  $\times 2.5$ , mid-LAD =  $\times 1.5$ , etc.). The final score was the sum of all weighted values. A Gensini score  $\geq 70\%$  indicated severe coronary stenosis.

### Ophthalmological Assessment

All patients underwent comprehensive fundus examination:

- Direct and indirect ophthalmoscopy for retinal vascular assessment.
- Fluorescein angiography performed using a Topcon TRC DX fundus camera with ImageNet 2000® digital system and a 5ml 10% sodium fluorescein dye injected intravenously. Sequential photographs were captured to document dye transit and areas of leakage or ischemia.
- Grading of diabetic retinopathy:
  - o Based on Early Treatment Diabetic Retinopathy Study (ETDRS) classification (mild, moderate, severe, or proliferative DR).
  - o Also classified according to the Scottish grading system for both retinopathy and maculopathy.

All patients underwent ophthalmologic and cardiac evaluations within a short time interval (usually within two weeks). Ophthalmologists and cardiologists were blinded to each other's findings to minimize observational bias.

Each patient's data were coded and entered into a computerized database for analysis. Both the severity of coronary disease (via Gensini and vessel scores) and diabetic retinopathy grades (via ETDRS and Scottish systems) were analyzed for correlations.

### Outcome Measures:

#### Primary Outcome:

To determine the correlation between the severity of diabetic retinopathy and the severity of coronary artery disease based on angiographic scoring systems (Gensini and vessel scores).

#### Secondary Outcomes:

1. To evaluate whether the presence or severity of DR could predict significant coronary lesions ( $\geq 70\%$  stenosis).
2. To assess whether DR can serve as an independent non-invasive marker for CHD risk in diabetic patients.

#### Statistical analysis:

All data were statistically analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were checked for normality using the Shapiro–Wilk test and expressed as mean  $\pm$  SD for normally distributed data or median (IQR) for skewed data. Qualitative variables were presented as numbers and percentages.

Comparisons between categorical variables were performed using the Chi-square test or Fisher's exact test when appropriate. Continuous variables were compared using the Independent-Samples t-test or Mann–Whitney U test, depending on data distribution. For multiple group comparisons, ANOVA or Kruskal–Wallis tests were applied.

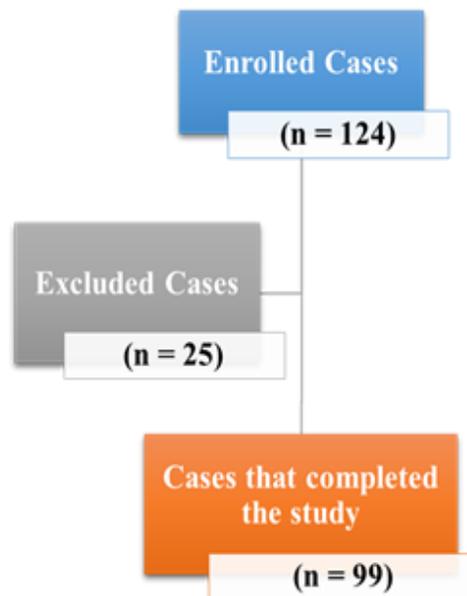
The correlation between the severity of diabetic retinopathy (DR) and coronary artery disease (CAD) (based on Gensini and vessel scores) was evaluated using Spearman's correlation coefficient. To determine independent predictors of severe coronary stenosis ( $\geq 70\%$ ), logistic regression analysis was performed, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

A p-value  $\leq 0.05$  was considered statistically significant, and  $p < 0.001$  was regarded as highly significant. Graphical illustrations such as bar and box plots were used to present the findings clearly.

## Results

### Demographic data

At the start of this study, 124 cases were enrolled. However, 25 cases were excluded due to incomplete data ( $n=11$ ) and missed follow up ( $n=14$ ). Therefore, this study was conducted on 99 participants.



**Figure 1:** Flow chart of the studied participants

(Table 1) Descriptive statistics data of the studied participants:

Qualitative data	N	%
<b>Sex:</b>		
• Male	53	53.5 %
• Female	46	46.5 %
<b>Smoking:</b>		
• Non-smoker	62	62.6 %
• Ex-smoker	14	14.1 %
• Current smoker	23	23.2 %
<b>Hypertension</b>	70	70.7 %
<b>Treatment of DM</b>		
• Oral	37	37.4 %
• Insulin	62	62.6 %
<b>BMI categories:</b>		
• Ideal	10	10.1 %
• Overweight	26	26.3 %
• Obese grade I	44	44.4 %
• Obese grade II	17	17.2 %
• Obese grade III	2	2 %
<b>Metabolic syndrome:</b>		
• IDF criteria	63	63.6 %
• NHLBI/AHA criteria	80	80.8 %

**Table 1a:** Clinicodemographic characteristic of the studied participants:

Qualitative data	N	%
<b>Presence of coronary lesions</b>	87	87.9 %
<b>Lesion 70% (1, 2 or 3 vessels with 70% lesion)</b>	75	75.8 %
<b>Number of major coronary vessels affected</b>		
• None	12	12.1 %
• One	38	38.4 %
• Two	30	30.3 %
• Three	19	19.2 %
<b>Gensini score groups</b>		
• ≤ 18	34	34.3 %
• > 18 to ≤ 42.4	32	32.2 %
• > 42.2	33	33.3 %

**Table 1b:** Characteristics of CAD of the studied participants

Qualitative data	N	%
<b>Presence of retinopathy</b>	49	49.5 %

<b>ETDRS classification of retinopathy</b>		
• A	13	26.5 %
• B	19	38.5 %
• C	8	16.3 %
• D	2	4.1 %
• E	4	8.2 %
• F	3	6.1 %
<b>Scottish grading of retinopathy &amp; maculopathy</b>		
• R0	50	50.5 %
• R1	13	13.1 %
• R2	19	19.2 %
• R3	10	10.1 %
• R4	7	7.1 %
• M0	75	75.8%
• M1	9	9.1%
• M2	15	15.2%

**(Table 1c):** Characteristics of the ocular lesion of the studied participants

Quantitative data	Normality	Mean $\pm$ SD	Median (IQR)
Age (years)	Normal distribution	55 $\pm$ 8	
Weight (kg)	Skewed distribution		90 (80 -96)
Height (cm)	Skewed distribution		169 (165 -173)
BMI (Kg/m <sup>2</sup> )	Normal distribution	30.9 $\pm$ 4.5	
Waist circumference (cm)	Normal distribution	100.5 $\pm$ 10	
Duration of diabetes (years)	Skewed distribution		12 (6 - 18)
Duration of hypertension (years)	Skewed distribution		8 (5 - 15)
Gensini score	Skewed distribution		26 (14 - 50)
Albumin (gm/dl)	Skewed distribution		3.9 (3.7 - 4.1)
Bilirubin (mg/dl)	Skewed distribution		0.9 (0.8 - 0.9)
ALT (U/ml)	Skewed distribution		27 (22 - 37)
AST (U/ml)	Skewed distribution		35 (22 - 45)
Serum creatinine (mg/dl)	Skewed distribution		0.9 (0.8 -1.1)
HDL (mg/dl)	Skewed distribution		40 (37 - 45)
LDL (mg/dl)	Skewed distribution		104 (95 -127)
TC (mg/dl)	Skewed distribution		175 (165 - 201)
TGs (mg/dl)	Skewed distribution		140 (100 -165)
FBG (mg/dl)	Skewed distribution		185 (156 - 222)
2 h PPBG (mg/dl)	Normal distribution	279.2 $\pm$ 70.8	
HbA1c %	Normal distribution	9.1 $\pm$ 1.2	

**Table 1 d:** Descriptive quantitative data of the studied participants

(Table 1): showing the characteristics of the studied 99 patients (53 males and 46 females). Their mean age (years)  $\pm$  SD was 55  $\pm$  8 (53.8  $\pm$  8.4 for males and 56.3  $\pm$  7.4 for females). All females were non-smokers while only 16 (30.2%) of males were non-smokers, 14 (26.4%) were ex-smokers and 23 (43.4%) were current smokers.

All the patient had T2DM with duration of diabetes (years) median (IQR) was 12 (6-18) years, 37 of them (37.4%) were on oral anti-diabetic drugs and 62 patients (62.6%) on insulin. 70 patients (70.7%) were hypertensive, with duration of hypertension (years) median (IQR) was 8 (5-15) years. Most of the patients were obese (89 patients), their mean BMI (kg/m<sup>2</sup>)  $\pm$  SD was 30  $\pm$  4.5

Of the 99 examined participants, 63 (63.6%) were diagnosed as MetS using IDF criteria. All were also diagnosed as MetS using NHLBI/AHA criteria. In addition, 17 participants (total N = 80) fulfilled the diagnostic criteria of MetS by NHLBI/AHA criteria. There was strong agreement between the two diagnostic criteria (Cohen's kappa = 0.587, P < 0.001) (Table 1a).

Among the 99 studied participants, 87 patients (87.9%) had coronary lesions and 75 patients (75.8%) of them had 70% lesion. Patients with one vessel disease were 12 (12.1%), two vessels disease were 30 patients (30.3%) and with three vessel disease were 19 patients (19.2%) (Table 1b).

Based on Kashani et al. (2016), studied cases were classified according to percentile 33.3 (18) and percentile 66.7 (42.4) into 3 ordered groups:

- Group (1): Score  $\leq$  18 (n = 34).
- Group (2): Score > 18 to  $\leq$  42.4 (n = 32).
- Group (3): Score > 42.4 (n = 33).

With median (IQR) of Gensini score were 26 (14 - 50)

Of the 99 examined participants, 49 (49.5%) were diagnosed to had DR. Using ETDRS classification of retinopathy, 13 patients (26.5%) were diagnosed to have mild NPDR, 19 (38.5%) with moderate NPDR, 8 (16.3%) with severe NPDR, 2 patients (4.1%) with very severe NPDR, 4 (8.2%) have early PDR and 3 patients (6.1%) have high risk PDR.

According to Scottish grading of retinopathy and maculopathy, 50 patients (50.5%) were diagnosed to have no retinopathy, 13 (13.1%) have mild NPDR, 19 (19.2%) have moderate NPDR, 10 (10.1%) have severe NPDR, 7 (7.1%) have PDR. Also, 75 (75.8%) were found to have no maculopathy, 9 (9.1%) focal maculopathy and 15 (15.2 %) diffuse maculopathy (Table 1c).

Scoring system	Correlation coefficient	p-value
Number of major vessels affected	0.314	< 0.001*
Lesion severity	0.142	0.114*
Gensini score	0.158	0.118**

(Table 2): Correlation of ETDRS classification of retinopathy and different scoring systems:

P value: \* Kendall's tau\_b, \*\*Spearman's correlation

This table shows a statistically significant positive correlation between the number of major vessels affected and ETDRS score. There was negligible positive correlation with both lesion severity and Gensini score which didn't achieve a statistical significance. Also, Cochran-Armitage

test was run to assess correlation of 70% lesion with ETDRS classification of retinopathy which revealed no significant correlation between 70% lesion and ETDRS (p=0.385).

Variable	With retinopathy (N=49)	Without retinopathy (N=50)	P value
Gensini score*	29 (18-49)	25 (7.5-50)	0.151
70% coronary lesion**	41 (83.7%)	34 (68%)	0.069
Number of lesions**			< 0.001
0	0 (0%)	12 (24%)	
1	17 (34.7%)	21 (42%)	
2	19 (38.8%)	11 (22%)	
3	13 (26.5%)	6 (12%)	

Table 3: Comparison of coronary artery disease between those with and without retinopathy

\*Presented as median (IQR) and compared by Mann-Whitney test. \*\*Presented as N (%) and compared by Chi-Square test (Column proportions compared by Z-score with Bonferroni adjustment).

This table shows no statistically significant difference in Gensini score (Z = -1.436, p = 0.151) and presence of 70% lesion ( $\chi^2 = 3.310$ , p = 0.069) between those with and without retinopathy. It shows, however, a statistically significant difference in the lesions' number ( $\chi^2 = 17.125$ , p < 0.001). While 24% of those without retinopathy had no 50% lesion, all

patients with retinopathy had varying numbers of coronary lesions (34.7%, 38.8% and 26.5%) had one, two and three lesions, respectively. The presence of coronary lesions in 100% of those with retinopathy and in 78% of those without retinopathy was statistically significant ( $\chi^2 = 13.382$ , p < 0.001).

Eye manifestation	Group (1) [n=34]	Group (2) [n=32]	Group (3) [n=33]	P value
<b>Retinopathy:</b>				0.323
R0	20 (58.8%)	15 (46.9%)	15 (45.5%)	
R1	5 (14.7%)	6 (18.8%)	2 (6.1%)	
R2	3 (8.8%)	7 (21.9%)	9 (27.3%)	
R3	4 (11.8%)	1 (3.1%)	5 (15.2%)	
R4	2 (5.9%)	3 (9.4%)	2 (6.1%)	
<b>Maculopathy:</b>				0.608
M0	27 (79.4%)	26 (81.3%)	22 (66.7%)	
M1	2 (5.9%)	3 (9.4%)	4 (12.1%)	
M2	5 (14.7%)	3 (9.4%)	7 (21.2%)	

Table 4: Scottish grading of retinopathy / Maculopathy in the three Gensini score groups

P value: Fisher's exact test.

This table shows no statistically significant difference in the distribution of retinopathy and maculopathy grades between the three Gensini score groups.

Eye manifestation	rs	P value
Retinopathy	0.164	0.105
Maculopathy	0.114	0.262

Table 5: Correlation between CAD severity and eye disease severity:

P value: Spearman's correlation. rs = Spearman's correlation coefficient.

This table shows no statistically significant correlation between Gensini score and Scottish grading of retinopathy and maculopathy.

Eye manifestation	Correlation coefficient	P value
-------------------	-------------------------	---------

Retinopathy	0.115	0.192
Maculopathy	0.108	0.245

**Table (5 b):** Correlation with Gensini score groups:

**P value:** Kendall's tau\_b.

This table shows no statistically significant correlation between Gensini score ordered groups and Scottish grading of retinopathy and maculopathy.

Eye manifestation	Correlation coefficient	P value
Retinopathy	0.169	0.200
Maculopathy	0.208	0.264

**P value:** Goodman and Kruskal's  $\gamma$ .

This table shows a weak positive association between Gensini score groups and Scottish Grading of retinopathy which was not statistically significant ( $\gamma = 0.169$ ,  $p = 0.200$ ) and a moderate, positive association

between Gensini score groups and Scottish Grading of maculopathy, which was not statistically significant as well ( $\gamma = 0.208$ ,  $p = 0.264$ ).

Eye manifestation	Without 70% lesion [n=24]	With 70% lesion [n=75]	P-value
<b>Retinopathy:</b>			0.332
R0	16 (66.7%)	34 (45.3%)	
R1	1 (4.2%)	12 (16%)	
R2	3 (12.5%)	16 (21.3%) a	
R3	3 (12.5%)	7 (9.3%) a	
R4	1 (4.2%) a	6 (8 %) a	
<b>Maculopathy:</b>			0.670
M0	20 (83.3%)	55 (73.3%)	
M1	1 (4.2%)	8 (10.7%)	
M2	3 (12.5%)	12 (16%)	

**Table 6:** Scottish grading of retinopathy / maculopathy in those with and without 70% lesion

**P value:** Fisher's exact test.

This table shows no statistically significant difference in the distribution of retinopathy and maculopathy grades between those with and without 70% lesion. Considering R as None (R0), early (R1-R2) and severe (R3-R4), there was also no statistically significant difference (p value was 0.134).

Also, Cochran-Armitage test was run to assess correlation of 70% lesion with Scottish grading of retinopathy/maculopathy in those with retinopathy (n=49) which revealed no significant correlation between 70% lesion and retinopathy (p=0.781), maculopathy (p=0.392).

Eye manifestation	No [n=13]	One [n=40]	Two [n=29]	Three [n=17]	P value
<b>Retinopathy:</b>					0.039
R0	13 (100%) a	21 (52.5%) b	10 (34.5%) b	6 (35.3%) b	
R1	0 (0%) a	4 (10%) a	7 (24.1%) a	2 (11.8%) a	
R2	0 (0%) a	9 (22.5%) a	7 (24.1%) a	3 (17.6%) a	
R3	0 (0%) a	3 (7.5%) a	3 (10.3%) a	4 (23.5%) a	
R4	0 (0%) a	3 (7.5%) a	2 (6.9%) a	2 (11.8%) a	
<b>Maculopathy:</b>					0.449
M0	13 (100%)	29 (72.5%)	21 (72.4%)	12 (70.6%)	
M1	0 (0%)	4 (10%)	4 (13.8%)	1 (5.9%)	
M2	0 (0%)	7 (17.5%)	4 (13.8%)	4 (23.5%)	

**Table 7:** Scottish grading of retinopathy / Maculopathy according to vessel score [number of significantly affected vessels (> 50% occlusion)]

**P value:** Fisher's exact test.

This table shows no statistically significant difference in the distribution of maculopathy grades according to number of significant vessels occluded. On the other hand, there was statistically significant difference in the distribution of retinopathy grades. R0 was reported in all cases

without significant vessel occlusion and in statistically significant lower proportions in those with any significant vessel occlusion (one, two or three).

Parameter	Without 70% lesion (n=24)	With 70% lesion (n=75)	Test of significance	
			$\chi^2 / Z / t$	P value
Age (years): Mean $\pm$ SD	55.6 $\pm$ 7.8	54.8 $\pm$ 8.1	t = 0.431	0.668
Sex: N (%)			$\chi^2 = 5.363$	0.021*
Male	7 (31.8%)	46 (59.7%)		
Female	15 (68.2%)	31 (40.3%)		
BMI (kg/m <sup>2</sup> ): Mean $\pm$ SD	31.5 $\pm$ 4.8	30.7 $\pm$ 4.5	FET	0.643**
Smoking: N (%)			FET	0.016**
Never smoke	21 (87.5%) a	41 (54.7%) b		

Ex-smoker	1 (4.2%) a	13 (17.3%) a		
Current smoker	2 (8.3%) a	21 (28%) b		
DM duration: Median (IQR)	11 (7 - 19.75)	12 (6 - 18)	Z = -0.303	0.762****
MetS: N (%)				
IDF criteria	19 (79.2%)	44 (58.7%) a	3.302	0.069*
NHLBI/AHA criteria	24 (100%)	56 (74.7%) b	FET	<b>0.005**</b>
A1c: Mean ± SD	9 ± 1.1	9.1 ± 1.2	t = -0.237	0.813***
TC: Median (IQR)	180 (170.25 - 201.25)	172 (165 - 201)	Z = -1.246	0.213****
LDL-C: Median (IQR)	110 (102 - 127.75)	101 (93 - 127.6)	Z = -1.548	0.122****
HDL-C: Median (IQR)	39.5 (35 - 43)	41 (38 - 45)	Z = -1.380	0.168****
TG: Median (IQR)	150 (109 - 176.75)	136 (100 - 165)	Z = -0.976	0.329****
Creatinine: Median (IQR)	0.9 (0.7 - 1.1)	0.9 (0.9 - 1.1)	Z = -1.006	0.315****
ALT: Median (IQR)	25 (23 - 34)	30 (20 - 40)	Z = -0.500	0.617****
AST: Median (IQR)	32 (22.8 - 42)	35 (22 - 45)	Z = -0.532	0.595****
Albumin: Median (IQR)	3.9 (3.73 - 4)	3.9 (3.7 - 4)	Z = -0.602	0.547****
Bilirubin: Median (IQR)	0.9 (0.8 - 1)	0.9 (0.8 - 0.9)	Z = -1.125	0.260****

**Table 8:** Comparisons of clinico-laboratory parameters between those with and without severe lesion (≥70% occlusion)

**P value:** \*Chi-Square test or \*\*Fisher’s exact test (FET) for qualitative data and \*\*\*Independent-Samples t-test or \*\*\*\*Mann-Whitney U test for quantitative data.

This table shows a statistically significantly higher proportions of male sex and current smokers in those with 70% lesion. It also shows a statistically significant lower proportion of MetS (NHLBI/AHA criteria)

in those with 70% lesion. considering smoking status as never smoking vs previous or current smoking,  $\chi^2 = 8.374$ , p value = 0.004.

Predictor	P value	COR	95% CI of COR
<b>Sex:</b>			
Female	<b>0.008</b>	R	R
Male		3.85	1.42 - 10.42
<b>Smoking status:</b>			
Never	<b>0.008</b>	R	R
Previous/current		5.81	1.59 - 21.14
<b>Retinopathy:</b>			
Absent	0.073	R	R
Present		2.41	0.92 - 6.32
<b>Retinopathy:</b>			
R0		R	R
R1-R2	0.052	3.29	0.99 - 10.99
R3-R4	0.511	1.53	0.43 - 5.44
<b>Retinopathy:</b>			
R0		R	R
R1	0.110	5.65	0.68 - 47.27
R2	0.188	2.51	0.64 - 9.87
R3	0.901	1.10	0.25 - 4.81
R4	0.355	2.82	0.31 - 25.45

**Table 9):** Univariable logistic regression analysis to predict the likelihood of severe lesion (≥70% occlusion):

**P value:** Binary logistic regression. COR=Crude Odds Ratio. R=Reference category.

This table shows that male sex and previous/current smoking are statistically significant predictors of the likelihood that participants will exhibit 70% lesion. It also shows that presence of retinopathy (regardless of its grade) is a barely significant predictor of the likelihood that participants will exhibit 70% lesion.

Predictors of the likelihood of occurrence of severe lesion (70% occlusion):

A multivariable binomial logistic regression was performed to ascertain the effects of male sex, previous / current smoking, and presence of retinopathy on the likelihood that participants have 70% lesion.

The logistic regression model was statistically significant,  $\chi^2 (3) = 14.471$ , p = 0.002. The model explained 20.3% (Nagelkerke R<sup>2</sup>) of the variance in 70% lesion and correctly classified 75.8% of cases with a sensitivity of 100% and positive predictive value of 75.8%.

Of the three predictor variables, only the presence of retinopathy (regardless of its grade) was statistically significant independent predictor of the likelihood of 70% lesion. Patients with retinopathy had 2.8 times higher odds to exhibit 70% lesion.

Predictor	P value	AOR	95% CI of AOR
<b>Sex:</b>			
Female	0.430	R	R
Male		1.70	0.46 - 6.33

<b>Smoking status:</b> Never	0.083	R	R
Previous/current		4.39	0.82 - 23.35
<b>Retinopathy:</b> Absent	<b>0.045</b>	R	R
Present		2.84	1.02 - 7.87

**Table 10:** Predictors of the likelihood of 70% lesion (Multivariate regression):

**P value:** Binary logistic regression. AOR= Adjusted Odds Ratio. R=Reference category.

Parameter	None	One	Two	Three	P1	P2
<b>Sex: N (%)</b>						
Male	4 (33.3%)	22 (57.9%)	17 (56.7%)	10 (52.6%)	0.497	0.515
Female	8 (66.7%)	16 (42.1%)	13 (43.3%)	9 (47.4%)		
<b>Smoking status: N (%)</b>						
Never	11 (91.7%)	19 (50%)	22 (73.3%)	10 (52.6%)	<b>0.025*</b>	0.365
Previous/ current	1 (8.3%)	19 (50%)	8 (26.7%)	9 (47.4%)		
<b>Retinopathy: N (%)</b>						
Absent	12 (100%)	21b (55.3%)	11 (36.7%)	6 b (31.6%)	<b>0.001</b>	<b>&lt; 0.001</b>
Present	0 (0%)	17 b (44.7%)	19 b (63.6%)	13 b (68.4%)		

**Table 11:** Comparisons of the number of vessels of the study participants:

**PI:** Chi-Square or \*Fisher’s exact test. **P2:** Cochran-Armitage test.

This table shows that there is statistically significant difference in the proportions of previous / current smoking and presence of retinopathy according to the number of vessels. No significant difference exists in sex distribution. Results of Cochran-Armitage test shows that the higher the number of affected vessels the higher the proportion of patients with retinopathy, but no correlation exists between the number of vessels affected and both sex and smoking status.

**Discussion**

Diabetic retinopathy (DR) and coronary artery disease (CAD) are two vascular complications of T2DM, where DR is an example of microangiopathy and CAD of macroangiopathy (Norgaz et al., 2005).

Coronary artery disease is a leading cause of mortality in diabetics (Aronson and Edelman, 2014). Diabetes has been considered a “cardiovascular risk equivalent”. Based on the Finnish study, in which diabetic patients with no evidence of CAD were equivalent to non-diabetic patients with previous coronary event in coronary mortality (Bertoluci and Rocha, 2017). While macroangiopathy is considered the main pathogenic mechanism of CAD in the general population, microangiopathy may have an eminent role in development of CAD in diabetics (Shereef and Kandeel, 2019).

Diabetic retinopathy is the most common and specific microvascular complication of diabetes and the leading cause of blindness worldwide (Fong et al., 2004). Even though, beyond visual impairment, the significance of DR is less recognized. Data from the Framingham Heart and Eye Study proposed that DR signs may reflect generalized microangiopathy that affects the myocardium in people with diabetes (Cheung et al., 2010). The Atherosclerosis Risk In Communities (ARIC) study showed that the presence of any signs of retinopathy was associated with 2-fold higher risk of incident CAD, 3-fold higher risk of fatal CAD (Cheung et al., 2007).

The similar risk factors between the DR and CVD, and the evidence that microvascular and macrovascular complications of DM share pathophysiological mechanisms that are related to hyperglycemia can explain the association between both complications (Control et al., 2005). Hyperglycemia promotes several intracellular signaling pathways leading to oxidative stress and overproduction of inflammatory markers that contribute to retinal endothelial dysfunction, increasing vascular permeability (the main event in the development of DR) (Roy et al., 2013). Also, associated with endothelial injury and chronic inflammation

which is the main pathological mechanism of atherosclerotic CVD (Fowler, 2011).

Furthermore, the microangiopathy affecting the retina may be occurring in other vascular beds, and the cardiovascular outcomes may be partially attributed to microvascular abnormalities in the myocardium and the arterial wall microcirculation (i.e., vasa vasorum). People with rapid progression in retinal pathology may be more predisposed to incident cardiovascular outcomes (Gerstein et al., 2013). In type 2 diabetic patients, the reduced coronary flow reserve (CFR), [an index of coronary microangiography], has been documented without presence of confirmed obstructive CAD and other myocardial disease (Yonaha et al., 2008).

Coronary artery disease patients with DR have poorer outcome, with high morbidity and mortality. (Ohno et al., 2008), (Pambianco et al., 2006). Also, they tend to have a poorer prognosis after CABG (Ono et al., 2002) or after percutaneous coronary intervention with insertion of drug eluting stents (Ohno et al., 2007).

So that, DR should be viewed as a biomarker of underlying deleterious effects of hyperglycemia on the systemic microcirculation (Cheung and Wong, 2008).

Our study was conducted on 99 diabetic patients with suspected CAD (53 male and 46 female) with age ranging from 20 to 70 years, who underwent elective coronary angiography. All participants were subjected to medical history, clinical examination, anthropometric measurements (weight, height, BMI), blood pressure, FBG, 2hPPBG, HbA1c, lipid profile, serum creatinine, Liver functions test, ECG, Echocardiography, coronary angiography, fundus examination using direct and indirect ophthalmoscope and Fluorescein angiography. Ethical approval was obtained and each subject signed a written informed consent.

Subjects with Age < 20 years and > 70 years old, history of cerebrovascular stroke, history of malignancy elsewhere in the body, history of chronic disease as chronic hepatic or renal disease, and other CVDs were excluded from the study.

The results of our study demonstrate that the presence of DR is a predictor of extent and severity of CAD detected by coronary angiography. Our findings are matched with several studies supporting the proposition that DR is significantly associated with CHD or increased cardiovascular events (Cheung et al., 2007) (Rosenson et al., 2011) (Rong et al., 2013).

We evaluated the relation between the degree and severity of DR with the severity of CAD. Severity of CHD was determined by Gensini score (Gensini, 1983), vessel score [number of coronary arteries with significant stenosis (using stenosis  $\geq 50\%$  cutoffs)] (Norgaz et al., 2005) and according to lesion severity  $\geq 70\%$  cutoffs considered have severe luminal narrowing (Gould, 2009).

Also, severity of DR was initially categorized following the ETDRS classification of retinopathy. Correlation of ETDRS classification and different coronary scoring systems shows a statistically significant positive correlation between the number of major vessels affected and ETDRS score. There was negligible positive correlation with both lesion severity and Gensini score which didn't achieve a statistical significance. Also, Cochran-Armitage test was run to assess correlation of 70% lesion with ETDRS classification of retinopathy which revealed no significant correlation between 70% lesion and ETDRS ( $p=0.385$ )

For the remaining analyses, the Scottish grading system for retinopathy and maculopathy was used because it offers a more practical and comprehensive classification. Unlike the ETDRS system, it includes maculopathy as a separate grading category and defines R0 (no retinopathy) and M0 (no maculopathy), allowing inclusion of patients without retinal disease. Additionally, the ETDRS grades (A-F) had very few cases in some categories, limiting statistical reliability. The simpler Scottish system provided better case distribution by combining grades C and D as severe NPDR and grades E and F as PDR, thus improving statistical strength and clinical clarity.

We found that there was no statistically significant difference in the distribution of retinopathy and maculopathy grades (using scottish grading) between the three Gensini score groups and between those with and without 70% lesion. Considering R as None (R0), early (R1-R2) and severe (R3-R4),  $p$  value was 0.134. Cochran-Armitage test was run to assess correlation of 70% lesion with Scottish grading of retinopathy/maculopathy in those with retinopathy ( $n=49$ ) which revealed no significant correlation between 70% lesion and retinopathy ( $p=0.781$ ), maculopathy ( $p=0.392$ )

Correlations between CAD severity and eye disease severity also was investigated by Spearman's correlation and Kendall's tau<sub>b</sub> test that show no statistically significant correlation between Gensini score, Gensini score ordered groups and Scottish grading of retinopathy and maculopathy. Using Goodman and Kruskal's  $\gamma$ , there was weak positive association between Gensini score groups and Scottish Grading of retinopathy which was not statistically significant ( $\gamma = 0.169$ ,  $p = 0.200$ ) and a moderate, positive association between Gensini score groups and Scottish Grading of maculopathy, which was not statistically significant as well ( $\gamma = 0.208$ ,  $p = 0.264$ ).

In contrary to our results, (Shereef and Kandeel, 2019) found that Patients with advanced DR had more severe CAD, more stenosis, and higher Gensini score than those with mild or no DR. Also, (Norgaz et al., 2005) and (Attia et al., 2020) were found that there was a highly significant positive correlation between the presence of DR and Gensini score [ $r = 0.881$ ,  $P < 0.001$ ]. This discrepancy may be due to the small number of subjects included in these studies ( $n = 50, 69$  respectively) and different methods of classification of retinopathy.

On other hand there was statistically significant difference in the distribution of retinopathy grades according to vessel score [number of significant vessels occluded (vessels having  $> 50\%$  stenosis)]. R0 (no retinopathy) was reported in all cases without significant vessel occlusion and in statistically significant lower proportions in those with any significant vessel. This result matched with (Sebaay, 2013) and (Attia et al., 2020) who found significant correlation between the presence of the DR and the number of diseased vessels [ $r = 0.532$   $P < 0.001$ ]. Similar results were found also by (Norgaz et al., 2005).

Um et al., (2016) found a significant increase in the number of vessels with significant stenosis ( $P = 0.011$ ), as the severity of DR increased. However, our study differs from this one that we evaluated the severity of CAD by coronary angiography, which is the gold standard tool for diagnosis of CAD.

Comparisons of clinico-laboratory parameters between those with and without 70% lesion shows a statistically significantly higher proportions of male sex in those with 70% lesion, in agreement with our results (Chiha et al., 2015) found that females have normal coronary arteries or less severe disease than males (the mean extent and vessel scores were higher in males than females), The pattern of CAD in females was found to be ultimately different from males (Merz et al., 2006), nuclear and magnetic resonance imaging have shown that females may have evidence of myocardial ischemia and microvascular dysfunction without presence of obstructive coronary disease (Bailey Merz and Pepine, 2011).

It also shows a statistically significantly higher proportions of current smokers in those with 70% lesion. (Yano et al., 2016) showed that smoking had significant association with the severity of coronary stenosis. current smokers are more likely to have vulnerable lipid-rich plaque, while former smokers have more calcified plaque (Abtahian et al., 2014), and this may explain the increased risk of acute cardiac events between smokers. Also, Low-grade inflammation may present in smokers and inflammation in blood vessels may be improved by cessation of smoking (Yasue et al., 2006).

Univariable logistic regression analysis to predict the likelihood of 70% lesion shows that male sex and previous/current smoking are statistically significant predictors of the likelihood that participants will exhibit 70% lesion. It also shows that presence of retinopathy (regardless of its grade) is a barely significant predictor of the likelihood that participants will exhibit 70% lesion. This result match with (Veeranna et al., 2010) who enrolled a cohort study on 631 patients; with age (range, 65-100 years), and 285 (45.2%) were men, they documented that male sex and smoking are predictors of the presence of obstructive CAD (significant stenosis  $\geq 70\%$ ).

A multivariable binomial logistic regression was performed to ascertain the effects of male sex, previous/current smoking, and presence of retinopathy on the likelihood that participants have 70% lesion.

Of the three predictor variables, only the presence of retinopathy (regardless of its grade) was statistically significant independent predictor of the likelihood of 70% lesion. Patients with retinopathy had 2.8 times higher odds to exhibit 70% lesion. This result was in parallel with prospective cohort study by (Cheung et al., 2007) as they stated that there is a 3-fold higher risk of fatal CHD associated with the presence of DR and this risk is independent of the glucose level or other cardiovascular risk factors. Also, (Norgaz et al., 2005) showed that the presence of DR was the only independent factor related to the severity score in multivariate analysis ( $r: 0.48$ ,  $P < 0.001$ ). (Gimeno-Orna et al., 2009) also demonstrate in his cohort study on type 2 diabetic patients that retinopathy is an independent risk marker for CVD in patients with T2DM.

The present results are also coinciding with (Kramer et al., 2011) meta-analysis of 20 epidemiologic studies and they found that patients with any degree of retinopathy die or experience a fatal or non-fatal cardiovascular event twice as patients with no retinopathy. This risk increases to be 4-fold higher in patients with advanced retinopathy independent of traditional risk factors. Also, they mentioned 4 studies carried out on 4,438 subject with T1DM (mean age 33 years and follow-up 12 years) and found that in the presence of any degree of retinopathy, there is a 3.5 to 4-fold increased risk of death and cardiovascular events and a 7-fold higher risk with advanced grades of retinopathy.

A study by (Kawasaki et al., 2013) on Japanese peoples with T2DM proved that the presence of DR is found to be associated with an increased

risk of CHD. Also, (Sasaki et al., 1997) in their cohort study on Japanese peoples with T2DM reported an association between any stage of DR and all-cause mortality; the present findings further illustrated that even a mild stage of DR is associated with a higher risk of CHD. In contrast, (Targher et al., 2008) found that the risk of incident CVD remained markedly increased in those with PDR/laser-treated retinopathy, but not in those with NPDR independent of other known cardiovascular risk factors.

Several researches have demonstrated that patients with DR are more probably to have defects in myocardial perfusion (Ioannidis et al., 2004) (Yoon et al., 2001), poorer CFR (Akasaka et al., 1997), and lower coronary collateral score (Celik et al., 2005) than those without DR. Furthermore, DR has been associated with higher degrees of coronary calcification (Yoshida et al., 1999) and more diffuse and severe stenosis of coronary arteries on coronary angiography (Norgaz et al., 2005). Another study reported that coronary microvascular abnormalities among diabetics with retinopathy is more profound than that among diabetics without retinopathy (Ono et al., 2002)

In addition, there are clinical researches suggested that the presence of retinopathy can be used as an indicator of silent myocardial ischemia and a guide for investigations and potentially treatment in diabetic patients with suspected CVD (Araz et al., 2004).

Liew et al., (2009) found that the presence of retinopathy increased the CHD mortality rate in patients with or without diabetes, suggesting that the presence of retinopathy, regardless of the patient diabetic state, may indicate underlying subclinical vascular disease. Retinopathy remained an independent predictor of CHD death in diabetic patients, after adjusting for cardiovascular risk factors.

These observations support that micro- and macrovascular complications of DM share common pathogenic mechanisms (Juutilainen et al., 2007) (Rema et al., 2004).

Prolonged hyperglycemia leads to the formation and accumulation of AGEs. AGEs induce angiogenic and thrombogenic vascular changes of endothelial cells, and a decrease in pericytes, the hallmarks of DR (Yamamoto et al., 2003). At the same time, an interaction between AGEs and their receptors in vascular smooth muscle cells, contribute to the stimulatory effect of DM on vascular smooth muscle cell proliferation that leads to progression of atherosclerosis (Norgaz et al., 2005). Therefore, the retinal microangiopathy may reflect an early subclinical abnormalities coronary or cerebral microvasculature and predispose to development of clinical cardiovascular events (Cheung et al., 2007).

## Limitations

Several limitations should be acknowledged. The study was conducted in a single center with a relatively small sample size, which may limit the generalizability of the findings. The cross-sectional design precludes establishing a causal relationship between the progression of DR and CHD. Additionally, the study included only patients with type 2 diabetes mellitus undergoing coronary angiography, potentially introducing selection bias toward individuals already suspected of having advanced cardiovascular disease. Other confounding variables—such as duration and control of hypertension, lipid-lowering therapy, or genetic factors—might have influenced both microvascular and macrovascular outcomes but were not fully adjusted for in the analysis.

## Conclusion

This study demonstrates a meaningful association between the severity of diabetic retinopathy and the extent of coronary artery disease in patients with diabetes mellitus. The presence of DR, irrespective of its grade, is an independent predictor of significant coronary lesions ( $\geq 70\%$  stenosis). These findings suggest that DR can serve as a clinical indicator of systemic vascular disease, supporting the concept that microvascular and macrovascular complications share common pathogenic pathways. Therefore, routine ophthalmologic screening in diabetic patients not only

aids in preventing visual loss but also provides valuable prognostic insight into cardiovascular health.

Based on the results, it is recommended that all diabetic patients undergo regular, comprehensive ophthalmologic examinations, and those with any degree of retinopathy should be considered for further cardiovascular evaluation—even in the absence of cardiac symptoms.

## Abbreviation Meaning

DR	Diabetic Retinopathy
CHD	Coronary Heart Disease
CAD	Coronary Artery Disease
T2DM	Type 2 Diabetes Mellitus
ETDRS	Early Treatment Diabetic Retinopathy Study
GFR	Glomerular Filtration Rate
BMI	Body Mass Index
ECG	Electrocardiography
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
FPG	Fasting Plasma Glucose
HbA1c	Hemoglobin A1c
TGs	Triglycerides
IDF	International Diabetes Federation
AHA/NHLBI	American Heart Association / National Heart, Lung, and Blood Institute
R0–R4, M0–M2	Scottish Grading System for Retinopathy/Maculopathy

## Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) of the Faculty of Medicine, Mansoura University prior to the commencement of the study. All participants provided written informed consent before inclusion.

## Acknowledgment

The authors would like to thank the staff of the Internal Medicine, Cardiology, and Ophthalmology Departments at Mansoura University for their continuous support during data collection and clinical evaluations. Special thanks to the Mansoura Specialized Medical Hospital for providing the facilities and resources necessary to complete this work.

## Author Contributions

All authors read and approved the final manuscript.

## Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this study.

## Confidentiality of Data

All collected data were anonymized prior to analysis. Patient identifiers were removed to ensure privacy. Data was stored securely and accessed only by the research team

## References

1. Abtahian F, Yonetsu T, Kato K, Jia H, Vergallo R, et al. (2014). Comparison by optical coherence tomography of the frequency

- of lipid coronary plaques in current smokers, former smokers, and nonsmokers. *Am J cardiol.* 114(5): 674-680.
2. Akasaka T, Yoshida K, Hozumi T, Takagi T, Kaji S, et al. (1997). Retinopathy identifies marked restriction of coronary flow reserve in patients with diabetes mellitus. *Journal of the American College of Cardiology.* 30(4): 935-941.
  3. Araz M, Celen Z, Akdemir I, Okan V (2004). Frequency of silent myocardial ischemia in type 2 diabetic patients and the relation with poor glycemic control. *Acta diabetologica.* 41(2): 38-43.
  4. Aronson DE, Edelman ER (2014). Coronary artery disease and diabetes mellitus. *Cardiology clinics.* 32(3): 439-455.
  5. Attia MA, Elraghy MI, Elgazar AF, Nayel SR. (2020). Correlation between diabetic retinopathy and the severity of coronary artery disease determined by coronary angiography in patients with type II diabetes mellitus. *International Journal of Medical Arts.* 2(1):204-10.
  6. Bairey Merz CN, Pepine CJ (2011). Syndrome x and microvascular coronary dysfunction. *Circulation.* 124(13): 1477-1480.
  7. Bertoluci MC, Rocha VZ (2017). Cardiovascular risk assessment in patients with diabetes. *Diabetology & Metabolic Syndrome.* 9(1): 25
  8. Celik T, Berdan ME, Iyisoy A, Kursaklioglu H, Turhan H, et al. (2005). Impaired coronary collateral vessel development in patients with proliferative diabetic retinopathy. *Clinical Cardiology: An International Indexed and Peer-Reviewed Journal for Advances in the Treatment of Cardiovascular Disease.* 28(8): 384-388.
  9. Cheng L, Barlis P, Gibson J, Colville D, Hutchinson A, et al. (2018). Microvascular retinopathy and angiographically-demonstrated coronary artery disease: A cross-sectional, observational study. *PLoS One.* 13(5):e0192350.
  10. Cheung N, Liew G, Wong TY. (2010). Current approaches to retinopathy as a predictor of cardiovascular risk. *Experimental approaches to diabetic retinopathy: Karger Publishers; p.* 203-219.
  11. Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, et al. (2007). Diabetic retinopathy and the risk of coronary heart disease: The atherosclerosis risk in communities study. *Diabetes care.* 30(7): 1742-1746.
  12. Cheung N, Wong TY (2008). Diabetic retinopathy and systemic vascular complications. *Progress in retinal and eye research.* 27(2): 161-176
  13. Chiha J, Mitchell P, Gopinath B, Plant AJ, Kovoov P, et al. (2015). Gender differences in the severity and extent of coronary artery disease. *IJC Heart & Vasculature.* 8: 161-166.
  14. Control D, Interventions CTEoD, Group CSR (2005). Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *New England Journal of Medicine.* 353(25): 2643-2653.
  15. Fong DS, Aiello LP, Ferris 3rd FL, Klein R (2004). Diabetic retinopathy. *Diabetes care.* 27(10): 2540-2553
  16. Fowler MJ (2011). Microvascular and macrovascular complications of diabetes. *Clinical diabetes.* 29(3): 116-122.
  17. Gensini GG (1983). A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol.* 51(3): 606.
  18. Gerstein HC, Ambrosius WT, Danis R, Ismail-Beigi F, Cushman W, Calles J, et al. (2013). Diabetic retinopathy, its progression, and incident cardiovascular events in the accord trial. *Diabetes care.* 36(5): 1266-1271.
  19. Gimeno-Orna JA, Faure-Nogueras E, Castro-Alonso FJ, Boned-Juliani B (2009). Ability of retinopathy to predict cardiovascular disease in patients with type 2 diabetes mellitus. *The American journal of cardiology.* 103(10): 1364-1367.
  20. Gould KL (2009). Does coronary flow trump coronary anatomy? *JACC: Cardiovascular Imaging.* 2(8): 1009-1023.
  21. Habib SA, Jibrán MS, Khan SB, Gul AM. (2019). Association of hypertensive retinopathy with angiographic severity of coronary artery disease determined by syntax score. *Journal of Ayub Medical College Abbottabad.* 31(2):189-191.
  22. Ioannidis G, Peppas M, Rontogianni P, Callifronas M, Papadimitriou C, et al. (2004). The concurrence of microalbuminuria and retinopathy with cardiovascular risk factors; reliable predictors of asymptomatic coronary artery disease in type 2 diabetes. *HORMONES-ATHENS-.* 3: 198-203.
  23. Jibrán MS, Zahid ZU, Habib SA. (2018). Diabetic retinopathy as a predictor of severity of coronary artery disease. *Khyber Medical University Journal.* 10(4):188-191.
  24. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M (2007). Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women. *Diabetes care.* 30(2): 292-299.
  25. Kawasaki R, Tanaka S, Tanaka S, Abe S, Sone H, et al. (2013). Risk of cardiovascular diseases is increased even with mild diabetic retinopathy: The japan diabetes complications study. *Ophthalmology.* 120(3): 574-582.
  26. Kramer CK, Rodrigues TC, Canani LH, Gross JL, et al. (2011). Diabetic retinopathy predicts all-cause mortality and cardiovascular events in both type 1 and 2 diabetes: Meta-analysis of observational studies. *Diabetes care.* 34(5): 1238-1244.
  27. Liew G, Wong T, Mitchell P, Cheung N, Wang JJ (2009). Retinopathy predicts coronary heart disease mortality. *Heart.* 95(5): 391-394.
  28. Merz CNB, Shaw LJ, Reis SE, Bittner V, Kelsey SF, et al. (2006). Insights from the NHLBI-sponsored women's ischemia syndrome evaluation (WISE) study: Part II: Gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *Journal of the American College of Cardiology.* 47(3 Supplement): S21-S29.
  29. Norgaz T, Hobikoglu G, Aksu H, Guveli A, Aksoy S, et al. (2005). Retinopathy is related to the angiographically detected severity and extent of coronary artery disease in patients with type 2 diabetes mellitus. *International heart journal.* 46(4): 639-646.
  30. Norgaz T, Hobikoglu G, Aksu H, Guveli A, Aksoy S, et al. (2005). Retinopathy is related to the angiographically detected severity and extent of coronary artery disease in patients with type 2 diabetes mellitus. *International heart journal.* 46(4): 639-646.
  31. Norgaz T, Hobikoglu G, Aksu H, Guveli A, Aksoy S, et al. (2005). Retinopathy is related to the angiographically detected severity and extent of coronary artery disease in patients with type 2 diabetes mellitus. *International heart journal.* 46(4): 639-646.
  32. Ohno T, Takamoto S, Ando J, Morita T, Fujita H, et al. (2007). Diabetic retinopathy and coronary implantation of sirolimus-eluting stents. *Journal of Interventional Cardiology.* 20(2): 122-131
  33. Ohno T, Takamoto S, Motomura N (2008). Diabetic retinopathy and coronary artery disease from the cardiac surgeon's perspective. *The Annals of thoracic surgery.* 85(2): 681-689.
  34. Ono T, Kobayashi J, Sasako Y, Bando K, Tagusari O, et al. (2002). The impact of diabetic retinopathy on long-term outcome following coronary artery bypass graft surgery. *Journal of the American College of Cardiology.* 40(3): 428-436.

35. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, et al. (2006). The 30-year natural history of type 1 diabetes complications: The pittsburgh epidemiology of diabetes complications study experience. *Diabetes*. 55(5): 1463-1469.
36. Rema M, Mohan V, Deepa R, Ravikumar R (2004). Association of carotid intima-media thickness and arterial stiffness with diabetic retinopathy: The chennai urban rural epidemiology study (cures-2). *Diabetes care*. 27(8): 1962-1967.
37. Rong J, Yu C-Q, Yang P, Chen J (2013). Association of retinopathy with coronary atherosclerosis determined by coronary 64-slice multidetector computed tomography angiography in type 2 diabetes. *Diabetes and Vascular Disease Research*. 10(2): 161-168.
38. Rosenson R, Fioretto P, Dodson P (2011). Does microvascular disease predict macrovascular events in type 2 diabetes? *Atherosclerosis*. 218(1): 13-18.
39. Roy MS, Janal MN, Crosby J, Donnelly R (2013). Inflammatory biomarkers and progression of diabetic retinopathy in african americans with type 1 diabetes. *Investigative ophthalmology & visual science*. 54(8): 5471-5480.
40. Sasaki A, Uehara M, Horiuchi N, Hasegawa K, Shimizu T (1997). A 15-year follow-up study of patients with non-insulin-dependent diabetes mellitus (NIDDM) in osaka, japan. Factors predictive of the prognosis of diabetic patients. *Diabetes research and clinical practice*. 36(1): 41-47.
41. Sebaay MEMOHMKME. (2013). Correlation between diabetic retinopathy and the severity of coronary artery disease in egyptian patients with type ii diabetes mellitus.
42. Shereef ASKandeel NT (2019). The relation between retinopathy grade and coronary artery disease in acute coronary syndrome diabetics. *Journal of Indian College of Cardiology*. 9(2): 83.
43. Shereef ASKandeel NT (2019). The relation between retinopathy grade and coronary artery disease in acute coronary syndrome diabetics. *Journal of Indian College of Cardiology*. 9(2): 83.
44. Targher G, Bertolini L, Zenari L, Lippi G, Pichiri I, et al. (2008). Diabetic retinopathy is associated with an increased incidence of cardiovascular events in type 2 diabetic patients. *Diabetic Medicine*. 25(1): 45-50.
45. Tavares CA, Rassi CH, Fahel MG, Wajchenberg BL, Rochitte CE, et al. (2016). Relationship between glycemic control and coronary artery disease severity, prevalence and plaque characteristics by computed tomography coronary angiography in asymptomatic type 2 diabetic patients. *The International Journal of Cardiovascular Imaging*. 32(10):1577-1585.
46. Um T, Lee DH, Kang J-W, Kim EY, Yoon YH (2016). The degree of diabetic retinopathy in patients with type 2 diabetes correlates with the presence and severity of coronary heart disease. *Journal of Korean Medical Science*. 31(8): 1292-1299.
47. Um T, Lee DH, Kang JW, Kim EY, Yoon YH. The degree of diabetic retinopathy in patients with type 2 diabetes correlates with the presence and severity of coronary heart disease. *Journal of Korean medical science*. 2016 Aug 1;31(8):1292-1299.
48. Veeranna V, Pradhan J, Niraj A, Fakhry H, Afonso L (2010). Traditional cardiovascular risk factors and severity of angiographic coronary artery disease in the elderly. *Prev Cardiol*. 13(3): 135-140.
49. Yamamoto Y, Sakurai S, Watanabe T, Yonekura H, Yamamoto H (2003). Possible participation of advanced glycation endproducts and their receptor system in the development of diabetic vascular complications. *Nihon Yakurigaku zasshi Folia Pharmacologica Japonica*. 121(1): 49-55.
50. Yano M, Miura S, Shiga Y, Miyase Y, Suematsu Y, et al. (2016). Association between smoking habits and severity of coronary stenosis as assessed by coronary computed tomography angiography. *Heart Vessels*. 31(7): 1061-1068.
51. Yasue H, Hirai N, Mizuno Y, Harada E, Itoh T, et al. (2006). Low-grade inflammation, thrombogenicity, and atherogenic lipid profile in cigarette smokers. *Circ J*. 70(1): 8-13.
52. Yonaha O, Matsubara T, Naruse K, Ishii H, Murohara T, et al. (2008). Effects of reduced coronary flow reserve on left ventricular function in type 2 diabetes. *Diabetes research and clinical practice*. 82(1): 98-103.
53. Yoon JK, Lee K-H, Park JM, Lee SH, Lee MK, et al. (2001). Usefulness of diabetic retinopathy as a marker of risk for thallium myocardial perfusion defects in non-insulin-dependent diabetes mellitus. *American journal of cardiology*. 87(4): 456-459.
54. Yoshida M, Takamatsu J, Yoshida S, Tanaka K, Takeda K, et al. (1999). Scores of coronary calcification determined by electron beam computed tomography are closely related to the extent of diabetes-specific complications. *Hormone and metabolic research*. 31(10): 558-563.



This work is licensed under Creative Commons Attribution 4.0 License

To Submit Your Article Click Here:

**Submit Manuscript**

DOI: [10.31579/2640-1045/224](https://doi.org/10.31579/2640-1045/224)

**Ready to submit your research? Choose Auctores and benefit from:**

- fast, convenient online submission
- rigorous peer review by experienced research in your field
- rapid publication on acceptance
- authors retain copyrights
- unique DOI for all articles
- immediate, unrestricted online access

At Auctores, research is always in progress.

Learn more <https://www.auctoresonline.org/journals/endocrinology-and-disorders>