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Research Article **Open Access Journal**

Dyslipidemia and Diabetic Retinopathy in Moroccans Type 2 Diabetics Patients: A Cross-Sectional Study

Sanae Chakdoufi [1], Amal Moumen[2], Anas Guerboub[3]

Corresponding Author: Sanae Chakdoufi

[1]Endocrinologist, Endocrinology and Diabetology Department, Mohammed V Military Hospital, Faculty of Medecine and Pharmacy, Mohammed V University, Rabat, Morocco.

[2]Assistant professor of Endocrinology and Metabolic Diseases, Endocrinology and Diabetology Department, Moulay Ismail Military Hospital of Meknes, Faculty of Medecine and Pharmacy, Sidi Mohamed Ben Abdellah University, Fes, Morocco.

[3]Assistant professor of Endocrinology and Metabolic Diseases, Endocrinology and Diabetology Department, Mohammed V Military Hospital, Faculty of Medecine and Pharmacy, Mohammed V University, Rabat, Morocco

Abstract:

Introduction: Diabetic retinopathy (DR) is a leading cause of blindness among adults under 60 years' old. The purpose of this study was to assess the factors associated with diabetic retinopathy in Type 2 diabetic subjects.

Methods: In a cross-sectional study, we enrolled type 2 diabetic patients from the endocrinology and diabetology department of the military hospital of Rabat assigned in two groups according to the presence or absence of DR. DR was diagnosed by fundus oculi. Fasting total cholesterol, triglyceride, HDL cholesterol, non-HDL cholesterol, and LDL cholesterol were assessed. A multiple logistic regression analysis was performed to identify independent factors associated with diabetic retinopathy.

Results: Two hundred and forty type 2 diabetic patients were enrolled. Age (p = 0.008), diabetes duration (p < 0.001), hypertension (p < 0.001), Microalbuminuria (p < 0.001), Dyslipidemia (p = 0.008), a non-HDL cholesterol > 1,3 g/l (p = 0.008) and serum triglycerides (p = 0.032) were significantly associated with DR. After adjusting for age, hypertension, diabetes duration and Microalbuminuria, total cholesterol (OR: 2.27; 95%IC: 1.02 – 5.07; p = 0.045), LDL cholesterol > 1 g/l (OR: 2.17; 95%IC: 1.09 – 4.34; p = 0,028) and non-HDL cholesterol > 1,3 g/l (OR: 2.46; 95%IC: 1.22 – 4.95; p = 0.012) were independent factors associated with DR.

Conclusion: Our data suggest that DR is independently associated with Serum lipids.

Key words: Diabetic retinopathy, Dyslipidemia, type 2 diabetes

Introduction

Diabetic Retinopathy (DR) is a classic diabetic microangiopathy that affect over one-third of diabetic patients [1]. With increasing prevalence of diabetes mellitus and increasing life span of diabetic patients, DR is set to be the leading global cause of Avoidable vision loss among young adults (20 to 65 years-old) [1]. Hypertension, diabetes duration and glycemic

control are the main risk factors of onset and progression of DR [1, 2].

Dyslipidemia is frequent among type 2 diabetes mellitus with increased triglyceride levels, and decreased High-density lipoprotein (HDL) Cholesterol levels. The main qualitative lipid abnormalities include large Very low-density lipoprotein (VLDL) particles, relatively rich in triglycerides, small dense Low-density lipoprotein (LDL) particles, glycation of apolipoproteins and increased susceptibility of LDL to oxidation [3 4]. Dyslipidemia could have a role in the pathogenesis of DR; however, findings from population-based studies and clinical trials are inconsistent [4,5]. The identification of a possible association between lipid anomalies and DR may have an interesting involvement in prevention and medical therapy of DR.

The purpose of this study was to assess the factors associated with diabetic retinopathy in Type 2 diabetic subjects specially the components of lipid anomalies.

Methods:

Population

In across-sectional study, we enrolled type 2 diabetic patients from hospitalized in the endocrinology and diabetology department of the military hospital of Rabat between January 2018 and August 2019 who had an ocular assessment, fundus oculi examination and lipid serum assessment.

Patients with already diagnosed DR, or with other ocular disease or with systemic disease that have ocular impact were excluded from this study.

Anthropometric data and cardiovascular risk factors were compiled from clinical charts. Total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol were measured by enzymatic technique after 12 hours of fasting. Non-HDL cholesterol was calculated the difference between total cholesterol and HDL cholesterol. Dyslipidemia was defined by LDL cholesterol > 1g/l and/or HDL cholesterol < 0.4 g/l and /or triglycerides > 1.5 g/l or the use of lipid lowering drugs.

Carotid atherosclerosis and lower limb diabetic arteritis were assessed by Doppler ultrasonography. Coronary Artery Disease was defined as history of previous myocardial infarction, or ischemic anomalies on the Electrocardiogram. Microalbuminuria was defined as urine albumin excretion rate of 30-300 mg/24h. The estimated glomerular filtration rate (GFR) was calculated using the "modification of diet in renal disease" equation and chronic kidney failure was defined by GFR < 60 ml/min/1.73m². Sensitive neuropathy was screened by DN4 questionnaire for neuropathic pain [6]. All patients had a detailed ocular assessment. Fundus examination under full mydriasis and based on the findings patients were grouped as having no signs of DR (Group 1), or having signs of DR (Group 2).

Statistical Analysis

Data were analyzed by SPSS software. Quantitative variables were expressed as mean ± standard deviation (total cholestrol, LDL cholesterol, non HDL cholesterol, HbA1c) or median and interquartiles range (age, diabetes duration, HDL cholesterol, triglycerides, plasma C-reactive protein (CRP)). Qualitative variables were expressed as numbers and percentages. The comparison of means was made by Student's t-test, the median by the Mann-Whitney test and the proportion by Khi-deux test. A multiple logistic regression analysis was performed to identify independent factors associated with DR. A *p*-value <0.1 was used to select variables included in the multiple logistic regression analysis. A *p*-value <0.05 was considered to be statistically significant.

Results:

240 type 2 diabetic patients were enrolled. The median of the patients' age was 54 (48 ;63) years-old with male predominance (51.3%). Anthropometric data and cardiovascular risk factors and dyslipidemia treatment are summarized in table 1.

Table 1: Baseline Characteristics of Patients

Characteristics	n=240)
Age M (IQ) °	4 (48 ; 63)
Sex§	
Male	23 (51,3%)
Female	17 (48,8%)
Diabetes duration M (IQ) °	0 (3 ; 16)
Smoking§	6 (27,5%)
Hypertension§	25 (52,1%)
Dyslipidemia§	88 (79,3%)
Obesity§	0 (25,5%)
Statines treatment§	20 (53,3%)
Fibrate treatment §	(0,4%)

° mediane (interquartiles)
§ numbers (pourcentages)

Fundus oculi examination was normal in 140 patients (58.3%). 76 patients (31.7%) had non-proliferative DR and 24 patients (10%) had proliferative DR.

Patients were than assigned in two groups:

Group 1 (n= 140 patients): including patients without DR

Group 2 (n = 100 patients): including patients with DR

Clinic and biologic data, lipid profile, and diabetic complications were compared between the 2 groups. Results are summarized in table 2. Factors associated with DR were : age (56 (52 ; 62,75) years-old vs 53 (43,25 ; 63) years-old, ***p* = 0.025**), diabetes duration (15 (10 ; 20) years vs 6 (2 ; 12) years ; ***p* < 0,001**), obesity (27 (32,9%) vs 23 (20.2%) ; ***p* = 0,043**), diabetic neuropathy (53 (53,5%) vs 39 (21,1%) ; ***p* < 0,001**), microalbuminuria (36 (40,9%) vs 22 (18,5%) ; ***p* < 0,001**) et kidney failure (18 (18,2%) vs 12 (8,6%) ; ***p* = 0,027**).

Regarding lipid profile, dyslipidemia (72 (72%) vs 102 (73,4%) ; ***p* = 0,007**), a non HDL cholesterol > 1,3 g/l (54 (58,7%) vs 55 (40,7%) ; ***p* = 0,008**) and triglycerides (1,24 (0,79 ; 1,85) vs 1,04 (0,75 ; 1,54) ; ***p* = 0,049**) were associated to DR.

Table 2: Comparison of demographic, biologic Characteristic and diabetes complications between patients with (group 2) and without (group 1) DR

	roup 1 (n = 140)	roup 2 (n = 100)	
Age (years) °	3 (43,25 ; 63)	6 (52 ; 62,75)	**,025**
Sexe (male) §	6 (54,3%)	7 (47%)	,266

Diabetes duration (years) ▫	(2 ; 12)	5 (10 ; 20)	**0,001**
Smoking §	8 (27,1%)	8 (28%)	,883
Hypertension §	3 (37,9%)	2 (72%)	**0,001**
Obesity§	3 (20,2%)	7 (32,9%)	**,043**
HbA1c (%)*	,82 ± 2,97	0,1 ± 2,41	,431
CRP (mg/l) ▫	,9 (1,2 ; 8)	(1,22 ; 5,97)	,554
Dyslipidemia§	02 (73,4%)	6 (87,8%)	**,007**
Total cholesterol (g/l)*	,72 ± 0,43	,83 ± 0,47	,095
LDL CT level (g/l)*	,04 ± 0,37	,10 ± 0,39	,309
LDL CT > 1 g/l§	1 (45,2%)	4 (58,1%)	,056
HDL CT level (g/l) ▫	,4 (0,34 ; 0,49)	,43 (0,36 ; 0,54)	,132
HDL CT ≤ 0,4 (g/l) §	2 (53,3%)	1 (44,6%)	,132
Non HDL CT level (g/l)*	,29 ± 0,43	,38 ± 0,46	,157
Non HDL CT > 1,3 g/l§	5 (40,7%)	4 (58,7%)	**,008**
Triglycerides (g/l) ▫	,04 (0,75 ; 1,54)	,24 (0,79 ; 1,85)	**,049**
Coronary artery disease§	7 (12,1%)	5 (15%)	,521
Carotid atherosclerosis §	1 (49,2%)	0 (54,5%)	,563
Lower limb diabetic arteritis §	0 (44,1%)	7 (48,2%)	,649
Diabetic Neuropathy§	9 (28,1%)	3 (53,5%)	**0,001**
Microalbuminuria§	2 (18,5%)	6 (40,9%)	**0,001**
Kidney failure§	2 (8,6%)	8 (18,2%)	**,027**

* mean ± standard deviation; ▫ mediane (interquartiles) ; § numbers (pourcentages) ;
CRP : C reactive protein ; LDL : low-density lipoprotein; HDL : High-density lipoprotein; CT : cholesterol

On the Univariate analysis, the factors associated with DR were : age (odds ratio (OR) : 1,03 ; 95% confidence interval (CI) [1,01 ; 1,05] ; p = 0,008), diabetes duration (OR : 1,13 ; 95% CI [1,09 ; 1,18], p < 0,001), hypertension (OR : 4,22 ; 95% CI [2,42 ; 7,34] ; p < 0,001), obesity (OR : 1,94 ; 95% CI [1,01 ; 3,71] ; p = 0,045), microalbuminuria (OR : 3,05 ; 95% CI [1,62 ; 5

;72] ; p < 0,001), kidney failure (OR : 2,37 ; 95% CI [1,08 ; 5,17] ; p = 0.03), diabetic neuropathy (OR : 2,95 ; 95% CI [1,72 ; 5,07] ; p < 0,001), dyslipidemia (OR : 2,6 ; 95% CI [1,27 ; 5,29] ; p = 0,008), a non HDL cholesterol > 1,3 g/l (OR : 2,06 ; 95% CI [1,20 ; 3,54] ; p = 0,008) and triglyceride (OR : 1,49 ; 95% CI [1,03 ; 2,17], p = 0,032) (Table 3).

Independent factors associated with DR in multivariate analysis, after adjustment for age, diabetes duration, hypertension and microalbuminuria, were total cholesterol (OR : 2,27 ; 95% CI [1,02 ; 5,07]; p = 0,045) ; an LDL cholesterol > 1 g/l (OR : 2,17 ; 95% CI [1,09 ; 4,34] ; p = 0,028) and a non HDL cholesterol > 1,3 g/l (OR : 2,46 ; 95% CI [1,22 ; 4,95] ; p = 0,012) (Table 3).

Table 3: Logistic regression for the factors associated with DR

	Univariate analysis			Multivariate analysis		
	OR	IC	*p*	OR	IC	*p*
Age	1,03	1,01 ; 1,05	**0,008**			
Sexe (Male)	0,74	0,44 ; 1,24	0,266			
Diabetes duration	1,13	1,09 ; 1,18	**< 0,001**			
Smoking	1,04	0,58 ; 1,85	0,883			
Hypertension	4,22	2,42 ; 7,34	**< 0,001**			
Obesity	1,94	1,01 ; 3,71	**0,045**			
HbA1c	1,03	0,94 ; 1,14	0,446			
CRP	0,99	0,97 ; 1,01	0,73			
Dyslipidemia *	2,6	1,27 ; 5,29	**0,008**	1,18	0,48 ; 2,88	0,711
Total cholesterol*	1,69	0,9 ; 3,14	0,097	2,27	1,02 ; 5,07	**0,045**
LDL CT > 1 g/l*	1,68	0,98 ; 2,86	0,057	2,17	1,09 ; 4,34	**0,028**
LDL CT level	1,45	0,70 ; 2,98	0,308			
HDL CT < 0,4 g/l*	0,70	0,41 ; 1,19	0,195	0,72	0,37 ; 1,41	0,344
HDL CT level	2,41	0,33 ; 17,6	0,385			
Non HDL CT > 1,3 g/l*	2,06	1,20 ; 3,54	**0,008**	2,46	1,22 ; 4,95	**0,012**
non HDL CT level	1,56	0,84 ; 2,91	0,158			
Triglycérides*	1,49	1,03 ; 2,17	**0,032**	1,28	0,81 ; 2,03	0,286
Coronary artery disease	1,27	0,6 ; 2,69	0,522			
Carotid atherosclerosis	1,23	0,6 ; 2,55	0,563			
Lower limb diabetic arteritis	1,17	0,58 ; 2,39	0,649			
Microalbuminuria	3,05	1,62 ; 5,72	**< 0,001**			
Kidney failure	2,37	1,08 ; 5,17	**0,03**			
DiabeticNeuropathy	2,95	1,72 ; 5,07	**< 0,001**			
statine	1,62	0,94 ; 2,78	0,079			

CRP : C reactive protein ; LDL : Low-density lipoprotein; HDL : High-density lipoprotein; CT : cholesterol
* Adjustment for age, diabetes duration, hypertension and microalbuminuria in the multiple logistic regression analysis

Discussion :

Total cholesterol, an LDL cholesterol > 1 g/l and a non-HDL cholesterol > 1.3 g/l were associated with DR in type 2 diabetic patients. This association is independent from the other classic risk factors of DR, which are diabetes duration and hypertension. On the other hand, diabetic control assessed by HbA1c was not associated with DR. This could be explained by selection of patient hospitalized for uncontrolled diabetes.

Several studies have focused on the association between DR and dyslipidemia.

Total cholesterol and HDL cholesterol were not associated to DR in The Wisconsin Epidemiologic

Study of Diabetic Retinopathy XIII [7]. In The Atherosclerosis Risk in Communities Study, the severity of DR was not associated to total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides in adult diabetic patients between 51 and 72 years-old [8]. Hove et al. found no significant association between the presence and severity of DR and triglycerides, HDL cholesterol, total cholesterol, Apoprotein (a) in an unselected population of danish type 2 diabetic patients [9]. The Multi-Ethnic Study of Atherosclerosis found that DR was not significantly associated with HDL-cholesterol, LDL-Cholesterol, and Triglyceride in 778 diabetic patients from multi-ethnic United State population aged from 45 to 85 years [10]. In The Beijing Eye Study, dyslipidemia was not significantly associated with the prevalence of DR in Chinese population [11] and the ADVANCE study did not find an association between HDL-Cholesterol level and the onset of DR in a cohort of 11,140 patients with type 2 diabetes [12].

On the other hand, five studies found an association between DR and dyslipidemia.

In popescu et al study which included 100 type 2 diabetic patient, total cholesterol (p = 0,011) and LDL cholesterol (p < 0,001) were significantly higher and HDL cholesterol was significantly lower (p = 0,001) in patient with DR compared to patient without DR [13]. However, in this study, there was no adjustment on the other risk factor of DR in the multivariable analysis.

In the Cardiovascular Health Study, a population-based cohort study, univariate analysis showed that DR was associated with higher plasma total and LDL cholesterol. After adjustment for age, sex and glycaemia, LDL cholesterol was an independent factor associated with DR (OR : 1,12 ; 95% CI [1,02 ; 1,23] ; p = 0,02) [14].

The Chennai Urban Rural Epidemiology Study, evaluated the association of serum lipids with DR in 1736 patients with type 2 diabetes. Total cholesterol (Standardised regression estimate (SRE) : 1,178 ; 95% CI [1,042 ; 1,331] ; p = 0,014), non HDL cholesterol (SRE : 1,169 ; 95% CI [1,04 ; 1,313] ; p = 0,012) and triglyceride (SRE : 1,292 ; 95% CI [1,136 ; 1,467] ; p = 0,001) were independent factors associated with DR after adjustment for age, sex and diabetes duration [5].

In a case-controlled study conducted by Sacks et al in type 2 diabetic patients from 13 counties, the OR for a retinopathy complication was 1.09 (95% CI, 1.02–1.16) per quintile of triglycerides and 0.93 (95% CI, 0.86–1.0) per quintile of HDL-Cholesterol. However, additional control for hypertension and HbA1c weakened these associations, and they did not remain significant [15].

A systematic review and meta-analysis of observational studies carried out by Zhou and *al* did not find obvious differences in triglycerides, total cholesterol, and HDL cholesterol levels between patients with DR and without DR. However, slightly higher LDL cholesterol levels were observed in the DR cases (mean difference (MD) 3.74mg/dL, 95% CI: 0.13–7.35, p = 0.04) [16].

Thus, results of different studies were controversial and no lipid anomaly was constantly associated with DR.

The mechanism for the associations between dyslipidemia and DR remains unclear. The accumulation of long-chain Fatty Acids are simultaneously converted into diacylglycerol the key activator of the protein kinase C [17]. The activation of protein kinase C contributes to the pathogenesis of DR in the form of differential synthesis of extracellular matrix proteins and extracellular matrix remodeling, enhanced release of angiogenic factors, endothelial and leukocyte dysfunction leading to capillary occlusion and leukostasis, and changes in blood flow to the retina [18]. The increase in blood viscosity and alterations in the fibrinolytic system occur in hyperlipidaemia and lead to the formation of hard exudates [19]. Recently, it has been suggested that blood-retina-barrier impaired by diabetes, allow extravasation of lipoproteins and their subsequent modification (i.e. oxidized and/or glycated) in tissue, hence their toxicity to the neighbouring retinal cells [20].

DR requires glycemic and blood pressure control sometimes difficult to achieve and local treatment used in advanced stage of DR and thus the need of

novel pharmacological treatment in the earlier stage of DR.

Our study suggest that dyslipidemia may be a potential therapeutic target in DR with an LDL cholesterol target < 1g/l and non-HDL cholesterol target < 1.3 g/l as proposed in cardiovascular prevention of diabetic patient.

Several studies showed an unexpected efficiency of some lipid-lowering drug. The STENO 2 study showed a significant reduction of DR progression with intensive control of dyslipidemia by statin and/or fibrate [21]. Gupta and al found that atorvastatin therapy in patients with type 2 diabetes reduces the severity of hard exudates and subfoveal lipid migration in clinically significant macular edema after laser treatment (p = 0.007) [22].

In the FIELD study, the requirement for first laser treatment for all retinopathy was significantly lower in the fenofibrate group than in the placebo group (hazard ratio [HR] 0,69; 95% CI 0,56 - 0,84; p = 0,0002; absolute risk reduction 1,5% [0,7–2,3]). In patients with pre-existing retinopathy, significantly fewer patients on fenofibrate had progression than did those on placebo (3,1% *vs* 14,6%; p = 0,004) on the ophthalmology substudy. Also, The risk of progression of retinopathy, development of macular edema, or one or more laser treatments (either eye) was significantly lower in the fenofibrate group than in the placebo group (HR : 0,66 ; 95% CI [0,47 ; 0,94] ; p = 0,022) [23]. The ACCORD-EYE study confirm the benefits of fenofibrate on DR with a reduction of 40% of the risk of DR progression in group with simvastatine-fenofibrate versus simvastatine-placebo (OR : 0,6 ; 95% CI [0,42 ; 0,87] ; p = 0,0056) [24]. This effect seemed unrelated to decreased serum levels of TG and cholesterol suggesting a pleoptrophic effect of fenofibrate. Peroxisome proliferator activated receptor (PPARα) agonists inhibit VEGF and thus decrease neovascularization and inflammation [25]. Data from FIELD and ACCORD eye trial suggest a potential benefice of fenofibrate treatment as an adjuvant treatment to reduce DR progression.

Otherwise our study present some limitations: it's a cross sectional study thus we cannot confirm that dyslipidemia is a risk factor of DR. antidiabetics, antihypertension and lipid-lowering drug may be effective and weakened the association between lipid anomalies and DR. In addition, the number of patient enrolled is limited.

Conclusion

Several data from different studies on the association between dyslipidemia and DR and the result of trials suggest the benefice of an intensive control of dyslipidemia by eventually associating a fibrate treatment in prevention and optimization of DR medical treatment. Further prospective multicentric studies are required to explore more this association and for defining the indication of lipid lowering drug and the target of different lipid fraction in medical treatment of DR;

Competing interests: authors declare that they have no conflict of interest

Key Points

- Total cholesterol, an LDL cholesterol > 1 g/l and a non-HDL cholesterol > 1.3 g/l were associated with DR in type 2 diabetic patients.
- This association is independent from the other classic risk factors of DR, which are diabetes duration and hypertension.
- Dyslipidemia may be a potential therapeutic target in DR with an LDL cholesterol target < 1g/l and non-HDL cholesterol target < 1.3 g/l as proposed in cardiovascular prevention of diabetic patient.

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