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High HDL cholesterol: A risk factor for diabetic retinopathy? Findings from NO BLIND study

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ABSTRACT

Aims: To assess the correlation between diabetic retinopathy (DR) and potential risk factors, as well as the relationship between DR and the other complications of diabetes, in a real-life population of type 2 diabetes patients recruited in several centres in Italy.

Methods: The NO BLIND is a cross-sectional, multicentre, observational study, which involved nine public outpatient clinics in Italy. The patients were assessed for eligibility from November 2016 till November 2017. Those enrolled underwent standard *fundus oculi* exam. Clinical and laboratory data were also collected.

Results: 2068 T2DM underwent *fundus oculi* exam. 435 received diagnosis of diabetic retinopathy (21%). Diabetic retinopathy was independently associated with HDL cholesterol (O.R.: 1.042; 95% C.I.: 1.012–1.109; $p = 0.004$), Albumin Excretion Rate (AER) (O.R.: 1.001; 95% C.I.: 1.000–1.002; $p = 0.034$) and GFR (O.R.: 1.159; 95% C.I.: 1.039–1.294; $p = 0.008$). HDL cholesterol values were hence split in two classes according to a potential cut-off (40 mg/dL), as defined by the ROC curve. Following analysis confirmed the association between DR and high HDL values ($p = 0.032$). Somatic neuropathy and diabetic ulcer were independently related with DR ($p < 0.001$ and $p = 0.012$, respectively).

Conclusions: A novel relationship between high HDL cholesterol and DR was observed.

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1. Introduction

Diabetic retinopathy (DR) represents the most spread ophthalmic diabetes mellitus complication (DM). There is a worldwide epidemic of diabetes, which has led to an outbreak of diabetic retinopathy (DR) [1].

Several epidemiologic studies in different geographic areas established DR as the main cause of blindness among working age adults, in Italy as well as in many other industrialized Countries [2,3].

The assessment of risk factors, as well as of other complications of diabetes, may help in both primary and secondary prevention of DR.

According to several studies, the main risk factors associated both with an earlier onset and a more rapid progression of the disease are diabetes duration, high glycated haemoglobin (HbA1c), and hypertension, in patients with type 2 diabetes (T2DM) [4,5], as well as microalbuminuria. These findings were all confirmed by the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), in particular for what concerns the progression to the proliferative forms of DR (PDR) [6]. In particular, an optimized glycaemic control demonstrated effective in reducing both new onset DR and its progression, though not preventing from a severe visual damage [7,8]. Less is known instead about the relationship between lipid serum levels and DR onset.

As established by the most recent literature of the last two decades, an interesting data regards the correlation between diabetic retinopathy and both the microangiopathic complications of diabetes (e.g., diabetic nephropathy and neuropathy) [9] and diabetic macroangiopathies (e.g., the cardiovascular risk) [10–12].

On these bases, our study aims to assess, in a real-life setting of patients with type 2 diabetes mellitus recruited in several centres in Italy (No BLIND study), the correlation between diabetic retinopathy and risk factors as well as the relationship with the other diabetes chronic complications.

2. Material and methods

2.1. Design of the study

The NO BLIND is a cross-sectional, multicentre, observational study. Nine public outpatient clinics of the South of Italy were involved in the study, whose first aim was the screening of Diabetic Retinopathy by telemedicine [13].

2210 patients were assessed for eligibility from November 2016 till November 2017.

Patients were included in the study according to the following criteria. First, we enrolled women/men aged >14 years, as a consequence of the fact that all participating centres were diabetic centres for the adults (patients with diabetes <14 years are usually followed by paediatrics diabetologists. In addition to this, DR below 14 years is extremely rare). Second, T2DM diagnosis had to be definite, based on the American Diabetes Association criteria [14]. Other inclusion criteria were: any therapy with anti-hyperglycaemic drugs (both oral and/or subcutaneous); either presence or absence of chronic complications of diabetes; whatever degree of glycaemic compensation (expressed as HbA1c, % - mmol/mol); any comorbidity.

Exclusion criteria were instead the following: patients aged <14 years, subjects with T1DM, subjects who did not provide the informed consent to the study and subjects with any other ocular pathology except DR.

We decided to include only T2DM patients in order to have the most homogeneous population as possible.

All patients enrolled in the study underwent a screening in telemedicine by photos performed in myosis with a digital ophthalmoscope (MiiS Horus Scope DEC 100, Digital Eye-fundus Camera, Medimaging Integrated Solution Inc. Brussels, Belgium). All photos were performed in a dark setting (<5 lux), in order for the pupil to have a sufficient diameter even though without pharmacological dilation (≥4 mm). All data were thus confirmed by traditional *fundus oculi* exam in mydriasis by a second expert ophthalmologist. DR was graded into non-proliferative DR (NPDR) and proliferative DR (PDR). NPDR was furtherly graded into mild, moderate and severe [15].

The study was approved by the University of Campania Ethics Committee and was conforming to the 1976 Declaration of Helsinki and its later amendments.

2.2. Data collection form

Data were collected in a predefined electronical form, which each centre had to complete for every patient enrolled in the study. The Case Report Form included all the following parameters: sex, age, weight, BMI, waist circumference, HbA1c, diabetes duration, blood pressure, heart rate, total and HDL cholesterol, triglycerides, creatinine, albuminuria, smoke or smoking habit, macro-/micro-vascular complications (previous AMI, previous stroke, known diabetic ulcer, known somatic and autonomic neuropathy, known retinopathy), therapy (insulin, DPP-IV inhibitors, GLP-1 receptor agonist, SGLT2 inhibitors, sulfonylureas/glinides, metformin, antiplatelets, statins, ACE inhibitors, sartanics, beta blockers, alfa blockers, calcium antagonists, diuretics). Data about chronic diabetes complications were collected either by clinical records previously present in CRF or by new specific exams prescribed to the patient at the last visit. More specifically, as all patients were followed in secondary care structures, there it is a praxis to perform the diagnosis of peripheral arteriopathy through lower limbs eco-color doppler. The diagnosis of somatic neuropathy is instead usually done by a study of both the vibratory sensitivity (through the determination of the VPT) and the tactile sensitivity by monofilament. Finally, the autonomic neuropathy is usually diagnosed through the five cardiovascular tests of Ewing and a questionnaire on the autonomic neuropathy. All these data were registered in the clinical record of each patient and, based on these data, we could do the diagnosis.

2.3. Endpoints

The primary endpoint of the study was the assessment of the main risk factors involved in DR development, including anthropometric (age, sex, BMI, waist circumference), laboratory (HbA1c, creatinine, total, HDL and LDL cholesterol,

triglycerides, albuminuria) and clinical data (smoke, hypertension, heart rate). Secondary endpoint was the evaluation of the relationship between DR and diabetic chronic complications (acute myocardial infarction, peripheral arteriopathy, stroke, both somatic and autonomic known neuropathy, known diabetic ulcer), both singularly and as a composite variable (Acute Myocardial Infarction, Stroke and Peripheral arteriopathy).

2.4. Statistical analysis

Continuous variables data are shown as median and range interquartile range (in the case of non-normal covariates) or mean and standard deviation, whilst categorical variables as number and percentage. First of all we performed a univariate analysis. In particular, differences between groups were analysed by Fisher exact test or Chi-square test for categorical variables. Mann–Whitney U test or Kruskal–Wallis non parametric test were performed to compare continuous variables, in the case of non-normal covariates, whilst in case of normal distribution the t-Test was applied. We then executed a multivariate logistic regression analysis with the stepwise Wald statistic input, including variables resulted statistically significant at the univariate analysis ($p < 0.05$).

In addition, a ROC curve was computed to establish a potential cut-off for HDL cholesterol values. Further, a Kaplan-Meier analysis was performed, in order to assess the cumulative risk of diabetic retinopathy according to the duration of diabetes.

P values below 0.05 were considered statistically significant. All analyses were performed with the SPSS software (IBM, Armonk, New York), version 24 and R software (CRAN ® 3.3.4).

3. Results

3.1. General features of the study population

142 subjects (6.4%) were excluded from the study, as they did not meet the inclusion criteria. In particular 62 patients (3.1%) were excluded as they had T1DM, 25 subjects (1.1%) instead did not sign the informed consent to the study and, finally, 48 patients (2.2%) had cataract or any other ocular pathology. Hence, the final enrolled population of the study was of 2068 patients. Therefore, two thousands, sixty-eight subject (n = 2068) with type 2 diabetes mellitus (T2DM), regularly followed in outpatient clinics, underwent photos performed in myosis with a retinograph (evaluated by an expert in a reading centre). All patients, independently from the retinograph diagnosis, also subsequently performed a traditional *fundus oculi* exam in mydriasis to confirm the previous diagnosis. All examinations were done in a period of one year: from November 2016 till November 2017. Thus, diagnosis of DR was confirmed by two different ophthalmologists.

The study population was equally distributed for sex: 1051 males (50.2%) and 1017 females (49.8%), with a median age of 66 years [IQR: 57–73 years.]. As aforementioned, all patients had type 2 diabetes mellitus, with a median duration of 8 years. [IQR: 4–15 years.], a mean glycated haemoglobin (HbA1c) of 7.3% (56 mmol/mol) [SD: ±1.3%].

Non-fatal Major Adverse Cardiovascular Events (MACEs), which included Acute Myocardial Infarction (AMI), stroke and peripheral arteriopathy, occurred in about 25% of the study population. As for pharmacological therapy, instead, data both on diabetes therapy and all other drug therapies were collected. The enrolled subjects were prevalently under metformin therapy (62.9%). Moreover, more than a half of the study population took statins (54.8%).

Anthropometric, clinical, biochemical and pharmacological characteristics of the patients are shown in Table 1.

Finally, the *fundus oculi* exam hence allowed for a prevalence of DR in our population equal to the 21% (435 of 2068 patients), with a 4.78% (99 cases) of proliferative retinopathy, a 16.22% (336 cases) of non-proliferative retinopathy and a 5.97% (123 cases) of diabetic macular oedema (DME). Among cases of NPDR the 49.1% (165 cases) were classified as mild NPDR, 39.65% moderate (133 cases) and 11.25% severe (38 cases). All cases of DME were associated either with non-proliferative or proliferative DR.

3.2. Evaluation of DR risk factors

For what concerns the main risk factors for DR, in particular, age ($p < 0.001$), HbA1c ($p = 0.004$), diabetes duration ($p < 0.001$), HDL cholesterol ($p = 0.015$), creatinine ($p = 0.005$), Albumin Excretion Rate (AER) ($p < 0.001$) and glomerular filtration rate (GFR) ($p < 0.001$) revealed significantly associated with the presence of diabetic retinopathy. The multivariate logistic regression analysis, adjusted for HbA1c, age and diabetes duration, underlined as potential independent risk factors for Diabetic Retinopathy: HDL cholesterol (O.R.: 1.042; 95% C.I.: 1.012–1.109; $p = 0.004$), AER (O.R.: 1.001; 95% C.I.: 1.000–1.002; $p = 0.034$) and GFR (O.R.: 1.159; 95% C.I.: 1.039–1.294; $p = 0.008$). Odds ratios represent the increased risk for DR with every increase in one unit of HDL cholesterol, AER and glomerular filtrate, respectively. All data are shown in Table 2.

First, we performed a ROC curve to establish a potential cut-off for HDL, which was fixed at 40 mg/dL (sensitivity 69%; specificity 64%) (Fig. 1). HDL cholesterol values were hence split in two classes according to the found cut-off (<40 mg/dL and ≥40 mg/dL). The successive analysis with respect to the either positive or negative diagnosis of DR confirmed the association between DR and ≥40 mg/dL HDL values ($p = 0.032$). We also performed the analysis by splitting HDL values into three subgroups, according to the clinical practice: <30 mg/dL, between 30 and 60 mg/dL and >60 mg/dL. This analysis again confirmed the significant association between DR and, in particular, HDL >60 mg/dL ($p = 0.001$), as well as for values <30 mg/dL ($p = 0.003$), whilst the statistical significance was not reached for intermediate values between 30 and 60 mg/dL ($p = 0.204$).

In addition, we also performed an analysis aimed to assess the relationship between DR and HDL, according to the different gradings of NPDR (mild, moderate and severe) and PDR in relation to the different subgroups of HDL levels previously reported. We observed in particular that HDL levels >60 mg/dL highly correlates with PDR ($p < 0.001$). No difference was observed between mild and moderate NPDR, whilst there was a trend for what concerns severe NPDR ($p = 0.076$). Furthermore, no correlation was found with macular oedema.

Table 1 – Baseline characteristics of the entire cohort of study (n = 2068).

Parameter	
Age (years.), median [IQR]	66 [57–73]
Sex, n (%)	
M/F[a]	1051 (50.2)/ 1017 (49.8)
BMI[a] (kg/m^2), median [IQR]	29 [26–32.5]
Waist circumference (cm), mean ± SD	
M	102.9 ± 12.4
F	102.2 ± 14.6
Smoke, n (%)	610 (29.6)
HbA1c[a], %(mmol/mol), mean ± SD	7.3 (56) ± 1.3
Duration of diabetes (years.), median [IQR]	8 [4–15]
Blood pressure (mmHg), mean ± SD	
Diastolic	78.7 ± 7.5
Systolic	129.6 ± 13.1
Hypertension (cut-off ≥ 130/80), n (%)	1185 (58.5)
Hypertension (cut-off ≥ 140/90), n (%)	600 (29.6)
Heart Rate (bpm), mean ± SD	73.1 ± 6.9
Cholesterol (mg/dL), mean ± SD	
Total	176.8 ± 37.1
HDL[a]	46.7 ± 14
LDL[a]	101.4 ± 33.7
Triglycerides (mg/dL), median [IQR]	124 [93–173]
Creatinine (mg/dL), mean ± SD	0.92 ± 0.35
Glomerular filtrate (CDK-EPI), mean ± SD	80.2 ± 20.6
AER[a] (mg/die), median [IQR]	22 [15 – 45]
Previous AMI[a], n (%)	256 (12.4)
Previous stroke, n (%)	89 (4.3)
Peripheral Arteriopathy, n (%)	327 (19.1)
Non-fatal MACEs[a], n (%)	514 (24.9)
Diabetic Ulcer – Anamnesis, n (%)	56 (2.7)
Neuropathy, n (%)	
Somatic	392 (19)
Autonomic	54 (2.6)
Diabetes therapies, n (%)	
Insulin	544 (26.4)
DPP-IV inhibitors	507 (24.6)
GLP-1 agonists	95 (4.6)
SGLT2 inhibitors	61 (3)
Sulfonylureas/Glinides	499 (24.2)
Metformin	1299 (62.9)
Other pharmacological therapies, n (%)	995 (48.3)
Antiaggregant	1131 (54.8)
Statins	548 (26.6)
ACE inhibitors	643 (31.2)
Sartanics	545 (26.4)
Beta Blockers	387 (18.8)
Calcium antagonists	544 (26.4)
Diuretics	98 (4.8)
Alfa-lytic	
DR[a] diagnosis, n (%)	
Yes/No	435 (21)/1633 (79)

Data are expressed as either number and percentage, or median and interquartile range (IQR) or mean ± SD.

[a] M: Male; F: Female; SD: Standard Deviation; IQR: interquartile range; BMI: Body Mass Index; HbA1c: Glycated haemoglobin; MACEs: Major Advanced Cardiovascular Events; HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol; AER: Albumin Excretion Rate; DR: Diabetic Retinopathy.

Also diabetes duration has been further analysed through a Kaplan-Meier analysis in order to assess the cumulative risk of diabetic retinopathy according to the duration of diabetes. Duration of T2DM >10 years determined a risk of DR development 2.7 times higher than subjects with T2DM duration ≤10 years, for which the risk was about 0.6 higher ($p < 0.001$) (Fig. 2A). According to the literature on DR risk based on diabetes duration, we furtherly stratified our population in four groups: (i) T2DM <5 years, (ii) between 5 and 10 years; (iii) between 10 and 20 years and (iv) >20 years. The risk estimate showed a similar result. People with diabetes for more than 20 years have a 2.4 times higher risk to develop DR vs the 0.35, 0.51 and 1.3 of groups (i) to (iii), respectively ($p < 0.001$) (Fig. 2B).

3.3. *DR and the other chronic complications of diabetes*

We also assessed the relationship between diabetic retinopathy and other micro- and macroangiopathic complications of diabetes.

The univariate analysis shows a statistically significant relationship between all complications, both macro- and microangiopathic, and DR. Cardiovascular complications were also combined in the composite variable MACEs, which, as well, reached a high statistical significance.

Due to this, we performed two multivariate analyses to evaluate if one among all diabetes chronic complications could independently affect the development of DR. First, we considered all the single variables. From this analysis, only somatic neuropathy and peripheral arteriopathy appeared independently associated with the outcome ($p < 0.001$ and $p = 0.032$, respectively) and diabetic ulcer ($p = 0.044$). A second logistic regression was performed by using the composite variable MACEs in place of the single cardiovascular complications. At this step somatic neuropathy and diabetic ulcer confirmed as factors independently associated with DR ($p < 0.001$ and $p = 0.012$, respectively). All data are shown in Table 3.

4. Discussion

DR represents one of the major microangiopathic complications in diabetes and the leading cause of visual impairment in the working-age population of the Western world [16].

Actually, the relationship between DR and HDL cholesterol serum level appears not well clarified.

In a Case–Control study performed in 13 Countries, diabetic microangiopathy (in particular diabetic nephropathy) was associated with higher levels of plasma triglycerides and lower levels of high-density lipoprotein cholesterol among patients with good control of low-density lipoprotein cholesterol [17].

However, some RCTs (ACCORD and FIELD) demonstrated that in patients with dyslipidaemia, DR progression was slowed by fenofibrate to a similar degree to that observed for intensive treatment in the glycemia trial [18]. The beneficial effect of fenofibrate (micronized fenofibrate 200 mg/die)

Table 2 – Univariate and multivariate analysis of risk factors for DR in the study subpopulation (n = 2068).

Parameter	Univariate analysis Diabetic retinopathy			Multivariate analysis	
	Yes (n = 435)	No (n = 1633)	P	O.R. [95% C.I.]	P
Age (years.), median [IQR]	68 [60–75]	65 [56–72]	<0.001	1.015 [1.005–1.025]	0.003
Sex, n (%)			0.523		
M/F[a]	227 (52.2)/208 (47.8)	824 (50.5)/809 (49.5)			
BMI[a], median [IQR]	29 [26–32.7]	29 [26.2–32.5]	0.635		
Waist circumference (cm), mean ± SD	102.3 ± 13.1	102.6 ± 13.6	0.798		
Smoke, n (%)	120 (27.6)	490 (30.2)	0.291		
Hypertension, n (%)					
≥130/80	240 (56.6)	945 (59)	0.368		
≥140/90	130 (30.7)	470 (29.4)	0.601		
Heart rate (bpm), mean ± SD	73.2 ± 7.2	73.1 ± 6.8	0.766		
Duration of diabetes, median [IQR]	12 [6–21]	8 [3–13]	<0.001	1.052 [1.038–1.066]	<0.001
HbA1c[a], % (mmol/mol), mean ± SD	7.5 (58) ± 1.3	7.3 (56) ± 1.3	0.004	1.150 [1.044–1.266]	0.005
Cholesterol (mg/dL), mean ± SD					
Total	175.9 ± 38.1	177 ± 36.9	0.592		
HDL[a]	48.1 ± 13.8	46.3 ± 14	0.015	1.042 [1.012–1.109]	0.004
LDL[a]	99.7 ± 32.8	101.9 ± 33.9	0.251		
Triglycerides (mg/dL), median [IQR]	122 [87–169.2]	125 [94–173]	0.170		
Creatinine (mg/dL), mean ± SD	0.96 ± 0.41	0.91 ± 0.33	0.005	1.263 [0.815–1.958]	0.296
AER[a] (mg/die), median [IQR]	29 [16–66]	22 [14.1–42]	<0.001	1.001 [1.000–1.002]	0.034
Glomerular filtrate (CDK-EPI), mean ± SD	76.7 ± 21.8	81.1 ± 20.1	<0.001	1.159 [1.039–1.294]	0.008

Data are expressed ad either number and percentage or median and interquartile range (IQR) or mean ± SD.
[a] M: Male; F: Female; SD: Standard Deviation; IQR: interquartile range; BMI: Body Mass Index; HbA1c: Glycated haemoglobin; HDL: High Density Lipoprotein Cholesterol; LDL: Low Density Lipoprotein Cholesterol; AER: Albumin Excretion Rate; OR: Odds Ratio; CI: Confidence Interval.

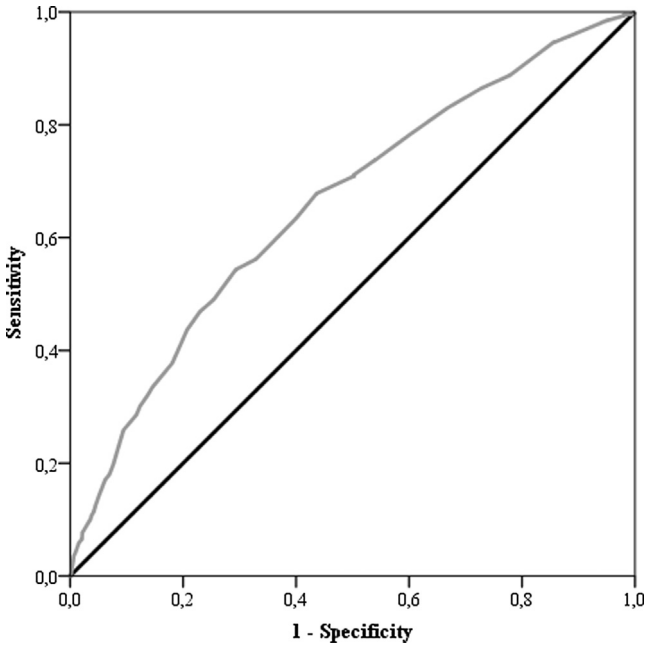

Fig. 1 – ROC curves describing the best cut-off level of for HDL levels.

appears to slow the progression of diabetic retinopathy when mild or moderate retinopathy is present. Instead, in particular in the ACCORD study, little or no effect of fenofibrate in subjects without DR was observed. Unlikely from the ACCORD study, the results of the FIELD study show benefits on DR progression which are not related to changes in lipid levels, as in subjects treated or not with a laser treatment there were no reported clinically relevant differences in mean plasma HDL cholesterol or triglycerides concentrations. Above all, DR was a tertiary endpoint in the FIELD, and its endpoints recorded in a substudy cohort of the ACCORD study population. Despite ADA Standards of Care strongly suggest to optimizing serum lipid control to slow DR progression [14], the efficacy of a fibrate in primary prevention of DR is not clear. Therefore, the exact beneficial action of fenofibrate as well as, and above all, higher HDL serum levels on DR still remains to be elucidated [18,19].

In this scenario, the most interesting result in our study is that high HDL cholesterol appeared as a potential independent risk factor for DR in multivariate logistic regression analysis. This finding does not find confirms in the previous literature, where strong evidence have been defined for what concerns an independent association of low values of HDL-cholesterol with both kidney disease and macroangiopathic complications of type 2 diabetes [17]. Instead, no evidence have been proven for its association with diabetic retinopathy [20]. In fact, other studies on this topic recruited patients different from the subjects we investigated. Wang NK et al., as well as Romero-Aroca et al. conducted studies on type 1 diabetics [21,22], which represent a very different population (as previously underlined) compared to type 2, whilst the little studies on T2DM patients show results not applicable to other patients with T2DM [23,24]. Moreover, further studies also established the association between HDL cholesterol and all-cause mortality as “U-shaped”, hence people with extremely high HDL may be at a higher risk of all-cause mortality [25]. This data was also confirmed in the CANHEART HDL

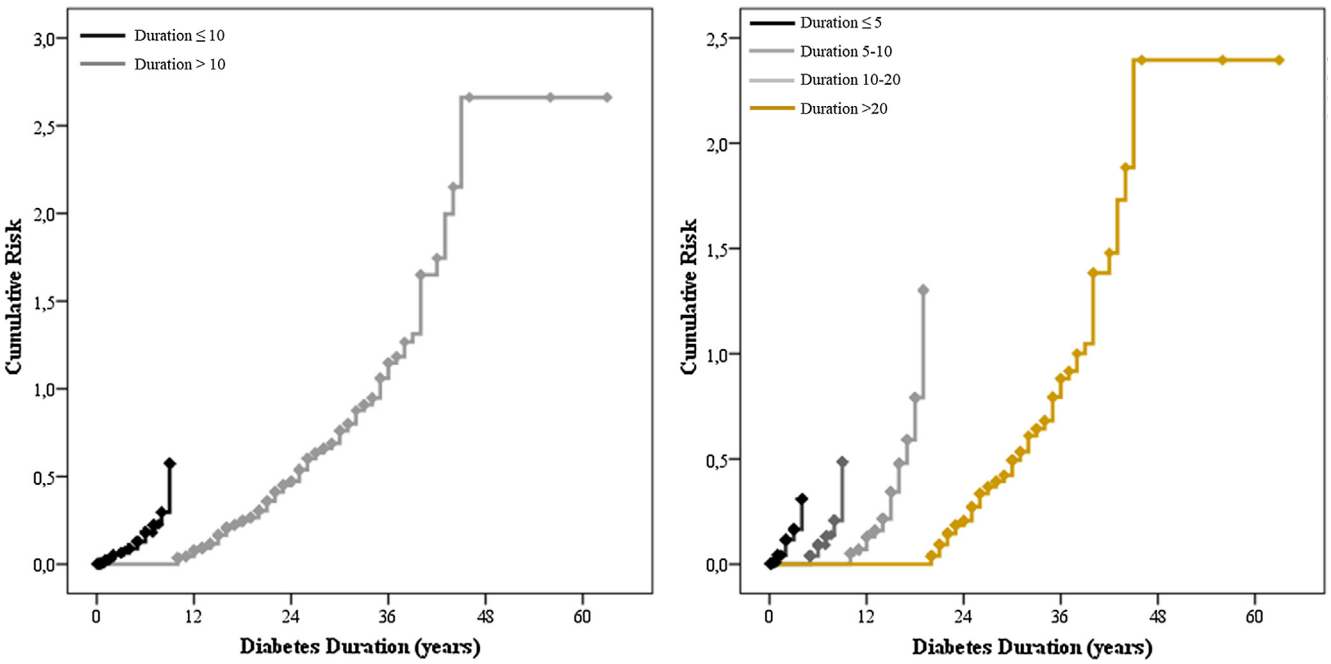

Fig. 2 – Kaplan-Meier curves showing (Panel A) the cumulative risk of diabetic retinopathy (DR) according to duration of type 2 diabetes ≤ or >10 years. and (Panel B) DR cumulative risk according to duration of type 2 diabetes, stratified in four groups: <5 years, between 5 and 10 years; between 10 and 20 years and >20 years.

Table 3 – Association between other chronic complications of diabetes and diabetic retinopathy in the study population: univariate and multivariate analysis (n = 2068).

Parameter	Univariate analysis Diabetic retinopathy			Multivariate analysis			
	Yes (n = 435)	No (n = 1633)	P	O.R. [95% C.I.]	P	O.R. [95% C.I.]	P
Previous AMI[a], n (%)			0.049	1.018 [0.719–1.441]	0.922		
Yes	66 (15.2)	190 (11.7)					
No	369 (84.8)	1439 (88.3)					
Previous stroke, n (%)			0.029	1.242 [0.722–2.138]	0.433		
Yes	27 (6.2)	62 (3.8)					
No	408 (93.8)	1566 (96.2)					
Peripheral Arteriopathy, n (%)			<0.001	1.720 [1.534–1.972]	0.032		
Yes	108 (29.3)	219 (16.3)					
No	260 (70.7)	1125 (83.7)					
Non-fatal MACEs[a], n (%)			<0.001			0.872 [0.670–1.133]	0.304
Yes	149 (34.3)	365 (22.4)					
No	286 (65.7)	1264 (77.6)					
Diabetic ulcer, n (%)			<0.001	1.543 [1.300–1.985]	0.044	1.481 [1.272–1.854]	0.012
Yes	29 (6.7)	27 (1.7)					
No	405 (93.3)	1600 (98.3)					
Somatic Neuropathy, n (%)			<0.001	1.392 [1.296–1.520]	<0.001	1.361 [1.280–1.466]	<0.001
Yes	153 (35.3)	239 (14.7)					
No	281 (64.7)	1387 (85.3)					
Autonomic Neuropathy, n (%)			<0.001	0.606 [0.315–1.166]	0.134	0.602 [0.335–1.083]	0.090
Yes	25 (5.7)	29 (1.8)					
No	410 (94.3)	1599 (98.2)					

[a] AMI: Acute Myocardial Infarction; MACEs: Major Adverse Cardiovascular Events; OR: Odds Ratio; CI: Confidence Interval.

Study [26]. In addition, most recent studies on 6000 patients have strengthened that HDL cholesterol values higher than 60 mg/dL were related to an increased risk of cardiovascular events [27,28]. Also another study showed that in high-risk T2DM patients with low LDL-C, higher baseline HDL-C predicted a higher CV risk, in contrast to patients with intermediate LDL-C [29].

Thus, larger populations and longitudinal studies could be helpful to further investigate the relationship between retinopathy and high HDL cholesterol levels.

Several hypotheses can be raised to explain this association between high HDL cholesterol and DR:

(a) residual confounding risk factors associated with both high HDL cholesterol and DR, not included in our multifactorially adjusted analyses; (b) alteration of the functionality of HDL in subjects with high HDL cholesterol; (c) this association could be an epiphenomenon of unknown pathophysiologic abnormality.

Our findings strengthen the correlation between micro- and macroangiopathy. Intriguingly, Avogaro et al. [30] have already suggested that a reduction in the burden of microangiopathy might bring to an improvement of cardiovascular outcomes in diabetes too. Moreover, this correlation between macro- and microangiopathy finds further confirmation in the literature with the independent association found with both amputations and peripheral arteriopathy [31].

About this correlation, another interesting data emerged most of all for what concerns the association found with both somatic and autonomic neuropathy, with only somatic neuropathy which revealed independently associated with DR development. Such an association have not been studied in depth in the literature yet, except for sporadic cases [9,32]. Consistently with our data, the authors found a statistically significant association between neuropathy and DR, hence they further investigated a more tight association between the different types of DR and neuropathy. Analogous data also emerged from several international trials [33–36].

No relationship was observed between DR and MACE, probably due to the sample size of our population. Hence, it would be interesting to investigate this topic more in depth in the next future.

Therefore, our findings not only confirm the clinical correlation between diabetes micro- and macroangiopathies, but also a relationship with high HDL values, recently observed only for CV outcomes.

This study, however, presents some limitations. First of all, the transversal observational real-life design of the study and, besides, the relatively small sample size. Moreover, ours is an observational clinical study, therefore it cannot offer pathophysiological interpretations of the observed results.

Nevertheless the multicentric design of the study and the DR prevalence of our population, which resembles both national and Western Countries rates, make our cohort representative.

Originally, this multicentre observational study identified as independent risk factors for DR in T2DM, besides the duration of diabetes, renal function and albuminuria and, not usual, a high HDL cholesterol too. This unexpected result was confirmed by the definition of a cut off of 40 mg/dL, with sufficient specificity and sensitivity, which significantly defined the risk of DR. Moreover, a highly significant association was observed between DR and HDL >60 mg/dL, as well as for HDL <30 mg/dL, hence defining a U-shaped association between HDL cholesterol and DR risk, as already recently observed in macrovascular disease and mortality too [25–28]. Actually, our findings are the first observation of an association between these extreme HDL values and a diabetic microangiopathy, as the DR.

The identification of subjects with a higher risk to develop DR could be much easier if we achieve an increased knowledge of DR risk factors. Accordingly, the ophthalmological control of these patients could be tighter.

In conclusion, these findings are original in the context of diabetic microangiopathy, but they were also recently observed in diabetic macroangiopathy, reinforcing the hypothesis of a wider correlation between the two types of vascular diabetic complications, perhaps involving new pathophysiological aspects that have to be investigated.

Finally, further prospective longitudinal studies, on larger sample sizes are needed to confirm these findings.

Author contributions

Conception and design: FC Sasso, A Gelso.

Development of methodology: FC Sasso, A Gelso, C Costagliola, V Bono.

Acquisition of data: V Bono, R Galiero, C Acierno, C de Sio, A Caturano, and NO BLIND Study Group.

Analysis and interpretation of data: PC Pafundi, FC Sasso.

Writing, review, and/or revision of the manuscript: PC Pafundi, FC Sasso, A Gelso, C Costagliola, V Bono, L Rinaldi, R Marfella, C Sardu, R Galiero, C Acierno, C de Sio, A Caturano, T Salvatore, LE Adinolfi.

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Conflict of interest

The authors declare that they have no conflict of interest.

Appendix

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.03.028.

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