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Evaluating the relation between serum apolipoprotein B (apo B), apolipoprotein A (apo A) and apo B/apo A ratio with diabetic retinopathy in a sample of type 2 Egyptian diabetic patient

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Abstract

Background Diabetic retinopathy (DR) is a chronic progressive, ocular disease affecting the retinal microvasculature accompanied by hyperglycaemia and different situations related to diabetes mellitus (DM) such as hypertension (HTN). Till now, the majority of researches demonstrated an insignificant correlation between lipid profile parameters and DR. Novel serum lipid markers (apolipoproteins) which are the protein portion of lipoproteins were recently linked to DR, and observed that the increased apo B and high apo B/apo A ratio accompanied by a higher possibility of proliferative DR.

Aim To assess the relation between novel serum lipid markers and various grades of DR in a sample of type 2 Egyptian diabetic cases.

Methods This study comprised 80 cases with type 2 diabetes mellitus (T2DM) divided into 3 groups: T2DM cases with proliferative diabetic retinopathy (PDR) (group I), T2DM cases with non-PDR (group II) and T2DM cases without DR as a control group (group III). Fasting plasma glucose (FPG), 2-h postprandial plasma glucose (2hpp), haemoglobinA1c (HbA1c), cholesterol (chol), triglycerides (TG), LDL, HDL and serum apolipoprotein A and B level. Complete medical history was taken from entire cases with a special focus on the duration of HTN and diabetes and full clinical examination (including BP and BMI).

Results There was a significant difference regarding serum apo B, apo B/apo A ratio, TG, total chol, LDL ($p<0.001$*), DM duration ($p=0.002$), HTN duration ($p=0.014$), SBP ($p=0.006$), DBP ($p=0.013$), BMI ($p=0.050$) and HbA1c ($p=0.025$), being higher in group I than group II than group III; also, there was a significant difference between them with regard to serum apo A ($p=0.010$), and HDL ($p=0.047$) being higher in group III than group II than group I.

On comparing group I with group II using Post hock Tukey's test there was a significant difference regarding serum apo B ($p=.023$) and apo B/apo A ratio ($p=.002$).

There was a statistically significant positive correlation between serum apo B/apo A ratio and diabetic duration ($r=0.248$), HTN d ($r=0.4$), HbA1c ($r=.47$), LDL ($r=0.68$), triglycerides ($r=0.52$), cholesterol ($r=0.70$) and a statistically

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significant negative correlation between serum apo B/apo A ratio and HDL (r=0.37) in all subjects. In addition, HTN duration was demonstrated to be the most independent factor affecting B/A ratio.

Conclusion Serum apo B and serum apo B/apo A ratio in diabetic cases are higher in the presence of retinopathy, triglycerides, total cholesterol, LDL, and HDL, and it is also higher in proliferative than non-proliferative diabetic retinopathy. The current study emphasizes on the potential correlation between the high serum apo B, serum apo B/apo A ratio and the advancement of DR.

Keywords Serum apolipoprotein B, Serum apolipoprotein A, Diabetic retinopathy, LDL, HDL, Cholesterol, Triglycerides

Introduction

Diabetic retinopathy (DR) has been considered as a frequent complication of diabetes mellitus (DM) featured by ischaemic microvascular retinal disease. In addition, it has been reported to be the primary cause of visual loss among cases with DM [1].

Injury from DR starts as NPDR and advances to PDR. NPDR is featured by alterations in the retinal blood vessels, which include an increase in permeability, capillary occlusion, microaneurysms, dot and blot haemorrhages and exudates. Ischaemia which is developed owing to abnormalities in retinal vascularity eventually ends in angiogenesis development (the main feature of PDR) [2]. Of note, the modifiable predisposing factors in the context of the development and advancement of DR and DME are hyperglycaemia and HTN [3].

Of note, hyperlipidaemia has been also considered as another potential predisposing factor in the context of DR. Till now, the majority of researches demonstrated no significant correlation between the lipid profile parameters and DR. In addition, the outcomes from epidemiologic researches emphasized on such correlations are not consistent [4].

Apolipoproteins are amphipathic molecules which adjust the transportation and distribution of lipoproteins, encouraging binding of lipoproteins to the receptors with a subsequent activation of lipid enzymes. Apolipoproteins accompanied by several diseases, comprising of diabetic macrovasculopathy and microvasculopathy and dysregulation of apolipoproteins A and B, are a concern in DR [5].

An important study was made to compare the correlation of DR with the values of apolipoproteins and with lipid profile in T2DM cases, which noticed that there is a potent correlation between serum apolipoproteins and the advancement and gravidity of DR in T2DM cases in comparison with traditional lipids [6].

In another important research aimed to evaluate the correlation between apo B and diabetic microvascular complication, the authors have displayed that apo B levels have a strong correlation with diabetic microvascular complications, and with the advancement of nephropathy grade, apo B level is significantly increased with the existence of at least one microvascular complication which associates positively with great values of apo B [7].

This study aims to estimate the novel serum lipid markers such as apolipoproteins in cases with T2DM with varying severity of DR to evaluate their role in the progression of DR.

Aim of the work

The aim of the work is to evaluate the relation between novel serum lipid markers and various grades of diabetic retinopathy in a sample of type 2 Egyptian diabetic cases.

Patients and methods

This study was conducted on 80 cases with T2DM whose ages range from 40 to 70 years old. They were allocated from the ophthalmology center at El-Demerdash Hospital within the period from March 2018 to September 2018. Before inclusion, consent was obtained from all cases following a proper description of the research design. They were subdivided into three groups: T2DM cases with PDR (group I), T2DM cases with NPDR (group II) and T2DM cases without retinopathy (control group) (group III). Cases with preceding eye surgeries; uveitis; the existence of different ocular or systemic diseases which include increased intraocular pressure, malignant tumours, renal dysfunction and hepatic disorders; previous history of using steroids; immunosuppressive agents or lipid-lowering agents; and those who received intraocular corticosteroids were excluded.

Entire cases were subjected to history taking with a special focus on HTN and DM duration, diabetic complications and symptoms of retinopathy and full clinical examination (including BP, BMI and WC and fundus examination).

Laboratory studies

Laboratory tests comprised FPG, 2-h postprandial plasma glucose (2hpp), HbA1c, total chol, TG, LDL, HDL and serum apolipoprotein A and B levels.

Measurement of HbA1c was performed by using Stanbio approach No.0350 "Quantitative colorimetric detection of Glycohaemoglobin in blood" and FBS; a 2-h postprandial plasma glucose was measured using an automatic glucose oxidase approach via Behring Diagnostics Reagents and lipid profile (total chol, HDL, LDL, TG) by colorimetric and fluorometric kit; and serum apolipoprotein A and B levels were measured using ELISA.

Statistical analysis

The collected data were analysed by utilizing the SPSS program. Quantitative data were expressed as mean±SD, while number and per cent (%) were utilized for qualitative data. Independent sample *t*-test was utilized to compare between 2 groups. ANOVA was utilized to compare among more than 2 groups. Post hoc test was utilized to recognize the LSD among the groups. In addition, *r* test was utilized in the context of data collection. Mann-Whitney *U* test was utilized to compare quantitative variables, in nonparametric data. Multivariate regression was performed to describe the independent predictors. A probability < 0.05 was considered significant.

Results

There were highly significant differences among all studied groups in terms of TG, total Chol, and apo B and B/A ratio ($P<.001$) and a statistically significant difference with regard to DM duration ($p=.002$), HTN duration ($p=.014$), SBP ($p=.006$), DBP ($p=0.013$), BMI ($p=0.050$), HbA1c ($p=.025$), LDL ($p=.001$), and HDL ($p=.047$) being higher in the patients with PDR than patients with NPDR in comparison with retinopathy free ones.

There was a difference among the studied groups in terms of apo A being greater among patients without DR than cases with NPDR than cases with PDR ($p=0.010$).

There was a statistically significant positive correlation between serum apo B/apo A ratio (B/A ratio) and DM duration ($r=.248$), HTN ($r=.4$), HBa1c ($r=.47$), LDL ($r=0.68$), triglycerides ($r=0.52$), and cholesterol ($r=0.70$) and a statistically significant negative correlation between serum apo B to serum apo A ratio and HDL ($r=0.37$). Multivariate regression analysis showed that hypertension duration (years) is an independent predictor of serum apo B/apo A ratio levels (Tables 1, 2 and 3).

Discussion

The current study demonstrated that serum apo B and B/A ratio were significantly higher in diabetic patients with DR than without retinopathy, and when they were further evaluated, it was found that serum apo B and B/A ratio were greater in DM cases with PDR than DM cases with NPDR ($p<0.008$), while apo A was significantly lower in group I, followed by group II and then group III ($p=0.010$). This agreed with Namitha et al. [8] who aimed to evaluate the ratio of apo B/apo A among the studied groups, healthy individuals, and diabetic patients without retinopathy and with diabetic retinopathy and found that there was a significant increase in apo B and apo B/apo A ratio while a significant decrease in apo A in a diabetic patient without retinopathy and with retinopathy than healthy individuals [8]. Results came in agreement also with Roxanne et al. [9] who studied 208 adult patients with T2DM and categorized them into four groups regarding the grade of retinopathy and presence or absence of macular oedema to evaluate the correlation between metabolic and inflammatory markers in the context of cases with DR. The study found that apo B and apo B/apo A ratios were the most significant predisposing factors for PDR and clinically significant macular oedema [9]. This came in the same line with Fatemeh Moosaie and his colleagues (2020) who have demonstrated that there was a negative correlation between ApoA and DR and a positive, strong correlation between ApoB and DR severity. Such correlations were independent of other predisposing factors of DR, which include albuminuria, duration of DM and kind of used therapeutic medication [10]. Additionally, this study demonstrated a significant positive correlation between serum apo B/A ratio in all studied subjects and LDL, triglycerides and cholesterol, HbA1C, and a significant negative correlation between serum apo B/A ratio and HDL. This agreed with Kumar et al. [11] who studied one hundred patients with T2DM. Groups are divided based on the A/C ratio, a correlation of dyslipidaemia was detected and apolipoprotein B was evaluated and found that apolipoprotein B was positively correlated with total Chol, TG, LDL-C, and non-HDL-C [11]. This came in disagreement with Ajith and his colleagues (2015) who recorded that there was no significant correlation between various lipid parameters and apolipoproteins with different stages of diabetic retinopathy, which may be due to the study participants being of other ethnicities (Indians) [12]. This study agreed also with John et al. (2008) who carried out the cross-sectional study and displayed that apo B values were significantly increased with an increase in HbA1c levels among cases with T2DM [13].

In this study, the multivariant regression analysis between the B/A ratio and other measured parameters shows that HTN duration is the only independent factor affecting the B/A ratio.

Conclusion

In summary, the study concluded that serum apo B and B/A ratio were higher and apo A is lower in T2DM cases with DR and a further significant in cases with diabetic

Table 1 Comparison of parameters among the studied groups

		Subgroups						Chi-square or ANOVA	
		Group I		Group II		Group III		X^2 or F	P-value
Sex	**Male**	17	56.67	8	26.67	3	15.00	10.623	**0.005***
	Female	13	43.33	22	73.33	17	85.00		
Diabetes TTT	**No**	0	0.00	0	0.00	1	5.00	6.980	0.323
	Insulin	14	46.67	8	26.67	7	35.00		
	Oral	5	16.67	11	36.67	5	25.00		
	Mixed	11	36.67	11	36.67	7	35.00		
Age (years)	**Range**	40–70		44–70		40–67		2.615	**0.080**
	Mean ±SD	58.567±8.472		57.000±8.162		52.450±5.586			
Diabetes duration (years)	**Range**	2–30		2–30		1–22		6.626	**0.002***
	Mean ±SD	14.900±6.635		14.667±7.595		8.350±5.905			
Hypertension duration (years)	**Range**	5–26		3–22		1–10		4.660	**0.014***
	Mean ±SD	11.409±5.704		10.313±5.522		5.300±3.831			
Systolic (mmHg)	**Range**	110–170		110–160		110–150		5.482	**0.006***
	Mean ±SD	141.667±16.626		135.667±15.013		127.500±11.180			
Diastolic (mmHg)	**Range**	60–110		70–100		70–100		4.641	**0.013***
	Mean ±SD	89.667±11.885		88.667±9.732		81.000±9.119			
BMI (kg/m^2)	**Range**	20.17–41.23		27.34–48.44		23.66–44.08		3.113	**0.050***
	Mean ±SD	32.083±5.039		35.204±4.650		34.770±5.975			
Waist circumference (cm)	**Range**	70–130		80–150		66–145		0.661	0.519
	Mean ±SD	99.167±12.815		102.767±14.818		103.500±17.491			
Fasting plasma glucose (mg/dl)	**Range**	110–300		100–350		88–400		0.803	0.452
	Mean ±SD	178.200±40.872		172.467±52.918		192.700±76.392			
2hpp (mg/dl)	**Range**	166–420		140–400		115–450		1.575	0.214
	Mean ±SD	286.167±62.590		252.233±72.642		259.600±99.827			
HbA1c %	**Range**	6.5–14		6–12		7–12		3.877	**0.025***
	Mean ±SD	10.583±1.712		9.787±1.549		9.360±1.474			
LD (mg/dl)	**Range**	87–210		78–230		75–143		7.766	**0.001***
	Mean ±SD	151.167±35.495		141.567±45.207		110.350±19.879			
HDL (mg/dl)	**Range**	28–77		23–60		38–71		3.190	**0.047***
	Mean ±SD	49.600±13.333		44.133±11.249		52.600±11.555			
TG (mg/dl)	**Range**	150–280		87–252		130–180		10.973	**<0.001***
	Mean ±SD	197.367±25.106		183.467±48.085		152.000±11.494			
Cholesterol (mg/dl)	**Range**	195–280		160–306		160–238		12.774	**<0.001***
	Mean ±SD	240.133±27.383		225.800±41.883		193.450±19.557			
Apo B (mg/dl)	**Range**	100–167		86–156		33–133		46.870	**<0.001***
	Mean ±SD	138.267±21.325		125.633±20.535		71.050±34.218			
Apo A (mg/dl)	**Range**	90–148		90–140		118–144		4.932	**0.010***
	Mean ±SD	114.933±15.739		122.533±15.883		127.450±7.817			
B/A ratio	**Range**	0.96–1.6		0.72–1.5		0.28–0.95		61.211	**<0.001***
	Mean ±SD	1.209±0.216		1.040±0.186		0.544±0.240			

**P*-value > 0.05: Non Significant (NS)

***P*-value < 0.05: Significant (S)

****P*-value < 0.01: Highly significant (HS)

Table 2 Correlation between apo B, apo A and B/A ratio and other measured parameters in studied subjects

Correlations						
Data	**Apo B (mg/dl)**		**Apo A (mg/dl)**		**B/A ratio**	
	r	***P*-value**	***r***	***P*-value**	***r***	***P*-value**
Age (years)	0.112	0.322	−0.143	0.206	0.163	0.149
Diabetes duration (years)	0.256	**0.022***	−0.035	0.757	0.248	**0.027***
Hypertension duration (years)	0.378	**0.008***	−0.102	0.491	0.418	**0.003***
Systolic (mmHg)	0.532	**<0.001***	−0.006	0.959	0.484	**<0.001***
Diastolic (mmHg)	0.437	**<0.001***	0.015	0.892	0.377	**0.001***
BMI (kg/m^2)	−0.126	0.265	0.079	0.487	−0.130	0.251
Waist circumference (cm)	−0.050	0.660	0.008	0.946	−0.033	0.768
Fasting plasma glucose (mg/dl)	−0.028	0.808	−0.102	0.368	0.006	0.958
2hpp (mg/dl)	0.124	0.273	−0.239	**0.033***	0.207	0.066
HbA1c %	0.388	**<0.001***	−0.258	**0.021***	0.470	**<0.001***
LDL (mg/dl)	0.599	**<0.001***	−0.331	**0.003***	0.681	**<0.001***
HDL (mg/dl)	−0.363	**0.001***	0.079	0.484	−0.378	**0.001***
TG (mg/dl)	0.490	**<0.001***	−0.162	0.151	0.528	**<0.001***
Cholesterol (mg/dl)	0.637	**<0.001***	−0.317	**0.004***	0.707	**<0.001***

**P*-value > 0.05: Non Significant (NS)

***P*-value < 0.05: Significant (S)

****P*-value < 0.01: Highly significant (HS)

Table 3 Multivariate regression analysis between serum apo B/apo A ratio and other measured parameters

All data	Unstandardized coefficients		Standardized coefficients	*t*	*P*-value
	B	**Std. Error**	**Beta**		
Diabetes duration (years)	−0.005	0.008	−0.124	−0.725	0.473
Hypertension duration (years)	0.021	0.010	0.382	2.045	**0.048***
Systolic blood pressure (mmHg)	−0.004	0.005	−0.140	−0.716	0.478
Diastolic blood pressure (mmHg)	0.003	0.005	0.068	0.490	0.627
HbA1c %	0.049	0.031	0.240	1.588	0.121
LDL (mg/dl)	0.003	0.006	0.373	0.610	0.546
HDL (mg/dl)	0.005	0.007	0.174	0.709	0.483
TG (mg/dl)	0.001	0.002	0.152	0.770	0.446
Cholesterol (mg/dl)	0.002	0.006	0.254	0.421	0.676

Dependent variable: B/A ratio

**P*-value > 0.05: Non Significant (NS)

***P*-value < 0.05: Significant (S)

****P*-value < 0.01: Highly significant (HS)

proliferative retinopathy than NPDR. Drawing attention to that apo b, apo A and apo B/apo A ratio seems to be a more beneficial biomarker for dyslipidaemia in DR than conventional lipid markers. In addition, a decrease in serum apo A and an increase in serum apo B and high apo B/apo A ratio appears to be accompanied by a higher possibility of PDR.

The limitation of this study is that the number of subjects comprised is relatively small so data can be inconclusive and additional researches with a large number of patients is needed.

Authors' contributions
This manuscript has been read and approved by all the authors, the requirements for authorship have been met, and this manuscript represents honest work.

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Availability of data and materials
All data are available to use.

Declarations

Competing interests
The authors declare that they have no competing interests.

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