Apolipoprotein B level and diabetic microvascular complications: is there a correlation?

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Introduction
Dyslipidemia has long been implicated in diabetic complications. However, many subgroups have been considered to be responsible. Furthermore, a cause and effect relationship has long been debated. Apolipoprotein B (Apo B) is an exact measure of the total number of very low-density lipoprotein and low-density lipoprotein particles; thus, total plasma Apo B is a reliable surrogate for actual low-density lipoprotein particle number irrespective of its size. Hence, it is a better indicator of the correlation between dyslipidemia and diabetic microvascular complications.

Aim of the work
Our aim is to study the correlation between Apo B and diabetic microvascular complications, namely, nephropathy and retinopathy.

Materials and methods
A cross sectional study was carried out of 56 diabetic patients, 36 men and 20 women, both type 1 and 2, who were chosen randomly from the outpatient Endocrinology Clinic in Cairo University. Serum creatinine, estimated glomerular filtration rate, urine albumin/creatinine ratio (A/C ratio), and Apo B levels were determined. Groups were divided according to the A/C ratio as follows: no proteinuria (A/C ratio <30 mg/g), incipient proteinuria (30–300 mg/g), and overt proteinuria (>300 mg/g). We performed fundus examination as well as fluorescein angiography in patients with retinopathy. Patients on dialysis, HBA1c more than 7.5, on lipid-lowering treatment, or with familial hyperlipidemia were excluded. Calculations were carried out using the SPSS v.10 statistical software.

Results
We found a significant positive correlation between Apo B levels and microvascular complications. Apo B was higher with overt nephropathy than incipient nephropathy (1.75 ± 0.38), and higher in patients with incipient nephropathy (1.4 ± 0.48) than in patients without nephropathy (1.02 ± 0.34, $P<0.01$).
A highly significant correlation was detected between the grades of retinopathy and the Apo B level. Finally, a significant positive correlation was detected between the presence of maculopathy and Apo B. Apo B levels were significantly higher in the presence of both nephropathy and retinopathy (1.26 ± 0.389) than in the absence of both complications (0.77 ± 0.361, $P<0.05$).

Conclusion
Apo B levels are strongly correlated to diabetic microvascular complications. The higher the degree of nephropathy, the higher the Apo B level. The presence of more than one microvascular complication correlates positively with high levels of Apo B. This suggests the possible use of Apo B as a sensitive biomarker of the presence of early diabetic microvascular complications.

Keywords:
apolipoprotein B, diabetic nephropathy, hyperlipidemia, retinopathy

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Introduction

Dyslipidemia has been considered to be a factor that plays a role in the progression of microvascular disease, especially in diabetes mellitus [1]. An 8-year follow-up study showed that low-density lipoprotein (LDL) was predictive of progression of diabetic nephropathy [2]. Moreover, microalbuminuria is often found in association with hyperlipidemia, especially in patients with diabetes and hypertension. Apolipoprotein B (Apo B) is the structural protein of all proatherogenic lipoproteins. Apo B-100 is the only lipoprotein that does not transfer among different lipid particles and is the only lipoprotein that could be elevated even in diabetic normolipidemic patients [3]. Thus, it could provide the best estimate of the total number of atherogenic particles even in the absence of hyperlipidemia. Furthermore, some studies suggested plasma Apo B concentration as a significant predictive factor of progressive renal failure [4].

It is likely that patients with diabetic retinopathy [5] are at a higher risk to progress to overt nephropathy. The eye is even considered the window of the kidney in type1 and type 2

diabetes. Hence, elevated lipids may increase the morbidity of macular edema and affect the severity of diabetic retinopathy.

Aim of work

Our aim is to study the correlation between Apo B and the various degrees of diabetic microvascular diseases, namely, nephropathy and retinopathy.

Materials and methods

A cross sectional study was carried out of 56 diabetic patients, 20 women and 36 men, who were chosen randomly from the Endocrinology Outpatient Clinic in Kasr El Ainy Hospital and were evaluated and graded according to their urinary albumin excretion rate as follows:

(1) Diabetics with no nephropathy [albumin to creatinine (A/C) ratio <30 mg/g].
(2) Diabetics with incipient nephropathy (A/C ratio = 30–299 mg/g).
(3) Diabetics with overt nephropathy (A/C ratio ≥ 300 mg/g).

Assessment of full history and full clinical examination were performed. Laboratory investigations were performed. These included serum creatinine, estimated glomerular filtration rate (eGFR), and A/C ratio in a spot urine collection, as well as serum Apo B. Ophthalmological examination was performed for visual acuity. Slit lamp examination was also performed. Fundus examination, using both a direct and an indirect ophthalmoscope, was performed. Fluorescein angiography was also performed to assess the degree of retinopathy.

Inclusion criteria

(1) Patients between 20 and 70 years of age.
(2) Type 1 diabetics for more than 20 years.
(3) Type 2 diabetics after 5 years of diagnosis.
(4) HBA1c between 6 and 7.5%.

Exclusion criteria

(1) Patients on regular hemodialysis (end-stage kidney disease).
(2) Patients with creatinine of at least 1.5 g/dl and or eGFR less than 40.
(3) HBA1c more than 7.5.
(4) Patients taking lipid-lowering drugs or a lipid-lowering agent in the previous 6 weeks.
(5) Patients with false albuminuria (UTI, CHF, fever).
(6) Patients with hypothyroidism, familial hyperlipidemia, familial hypercholesterolemia, and alcoholics, to avoid a false increase in apolipoproteins.

Statistical analysis

Our results were expressed as mean ± SD or numbers (%). Comparison between the mean values of two groups was carried out using an unpaired student's *t*-test. For more than two groups, the analysis of variance test was performed to compare the means. Comparison between categorical data [*n* (%)] was carried out using the χ^2-test. The correlation between continuous parameters was determined using Pearson's *r* correlation coefficient. If ordinal data were used, spearman's ρ correlation coefficient was calculated to assess correlation. A *P* value less than 0.05 was considered significant, whereas a *P* value less than 0.01 was considered highly significant. Calculations were carried out using the SPSS v.10 (IBM, USA) statistical software.

Results

Table 1 shows a comparison between the mean values of the study parameters in different stages of nephropathy. We detected a significant difference between groups of nephropathy in Apo B ($P<0.01$), albumin in urine ($P<0.01$), A/C ratio ($P<0.01$), eGFR (estimated by modification of diet in renal disease grading), and serum creatinine.

We found that estimated GFR was higher in patients with incipient nephropathy than in normoalbuminuric patients and the lowest in patients with overt nephropathy. As expected, serum creatinine showed a pattern that was reciprocal to eGFR, that is it was lower in patients with incipient nephropathy than in those with normoalbuminuria. Serum creatinine reached its maximum level in patients with overt nephropathy.

Figure 1 shows a positive correlation between Apo B level and severity of nephropathy, that is Apo B in patients with overt nephropathy was more than Apo B in patients with incipient nephropathy and this in turn was more than Apo B in normoalbuminuric diabetic patients.

Table 1 Comparison between the mean values of the study parameters in different groups of nephropathy using the analysis of variance test

	Stage of nephropathy (mean ± SD)			
	Normal (*N*=23)	Incipient (*N*=21)	Overt (*N*=12)	Significance *P*
Age (years)	51.4 ± 7.8	54.6 ± 8.8	54.7 ± 7	>0.05
Serum creatinine (mg/dl)	1.03 ± 0.23	0.93 ± 0.15	1.19 ± 0.3	<0.01
Albumin in urine (mg/l)	11.1 ± 8.3	64.2 ± 48.4	433.6 ± 163	<0.01
A/C ratio (mg/g)	10.9 ± 6.1	75.5 ± 39.8	528.9 ± 165.4	<0.01
eGFR by MDRD (grading)[a]	68.7 ± 17	70.3 ± 10.8	57.3 ± 13.6	<0.05
Apo B (g/l)	1.02 ± 0.34	1.4 ± 0.48	1.75 ± 0.38	<0.01

A/C, albumin/creatinine; Apo B, apolipoprotein B; eGFR, epidermal growth factor receptor; MDRD, modification of diet in renal disease.
[a]eGFR measured in ml/min/1.73 m.

We compared the mean levels of Apo B in groups of patients with no, single, or combined microvascular complications. As shown in Table 2, we found that the Apo B level increased in patients with one or more microvascular complications than in patients without microvascular complications. A significant increase in the mean values of Apo B occurred in patients with nephropathy (any degree) with/without retinopathy than in patients without nephropathy ($P<0.001$). The latter showed the highest significant difference.

Also, there was a significant increase in Apo B in patients with nephropathy only (but free from retinopathy) than in patients who did not have either retinopathy or nephropathy ($P<0.02$).

In addition, there was a significant increase in Apo B in patients with retinopathy (any degree) with/without nephropathy as compared with those without retinopathy ($P<0.02$).

Furthermore, there was a significant increase in Apo B in patients with both forms of complications (nephropathy and retinopathy) as compared with those without either of these complications ($P<0.05$).

In patients with nephropathy with/without retinopathy, the mean levels of Apo B were more statistically significant than in patients with nephropathy and without retinopathy, showing that a combination of both complications affects Apo B levels than in those with either complication alone.

Serum creatinine levels showed a significant correlation with serum Apo B levels ($r=0.295$; $P<0.05$). Moreover, urinary albumin levels showed a highly significant correlation with both serum Apo B levels ($r=0.519$; $P<0.01$) and the stage of nephropathy ($r=0.804$; $P<0.01$).

High Apo B is accompanied by a higher stage of nephropathy and more proteinuria. As shown in Table 3, the increase in Apo B is accompanied by a lower eGFR (especially at the overt nephropathy level).

Figure 2 shows a significant correlation between Apo B level and retinopathy grading. The higher the Apo B concentration, the higher the degree of retinopathy.

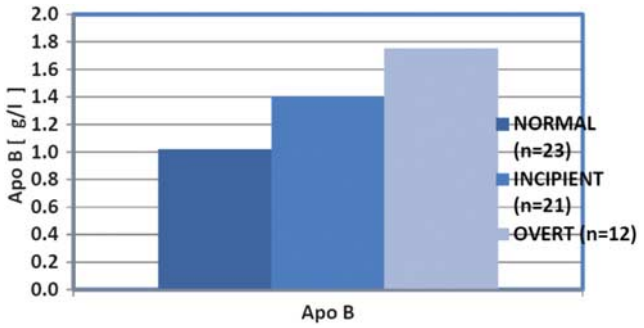
The mean values of the A/C ratio and Apo B were higher in patients with overt nephropathy than in those with incipient nephropathy. Apo B levels were also higher in patients with incipient nephropathy than in those who did not have nephropathy. As expected, estimated GFR reached its lowest value in patients with overt nephropathy and reached its maximum value in patients with incipient nephropathy. This could be attributed to the fact that the stage of incipient nephropathy is a stage of hyperfiltration.

Serum creatinine levels showed a positive significant correlation to serum Apo B levels. We found a significant negative correlation between eGFR (estimated by modification of diet in renal disease grading), Apo B, and A/C ratio (especially at the level of overt nephropathy).

A significant positive correlation was found between the stages of diabetic nephropathy to the grades of diabetic retinopathy. The macular changes, however, did not show a significant correlation to the stage of nephropathy.

A highly significant correlation was detected between the grades of retinopathy and the Apo B level. Finally, a

Figure 1



Apolipoprotein B (Apo B) levels in different stages of nephropathy.

Table 3 Correlation of epidermal growth factor receptor (estimated by MDRD grading) and other parameters (Pearson's correlation)

Parameters	*R*	*P*
Apo B (g/l)	−0.343[a]	0.01
A/C ratio (mg/g)	−0.264[b]	0.049
Albumin in urine (mg/l)	−0.265[b]	0.048
Creatinine in urine (mg/dl)	0.166	0.223
Creatinine (serum) (mg/dl)	0.166	0.223

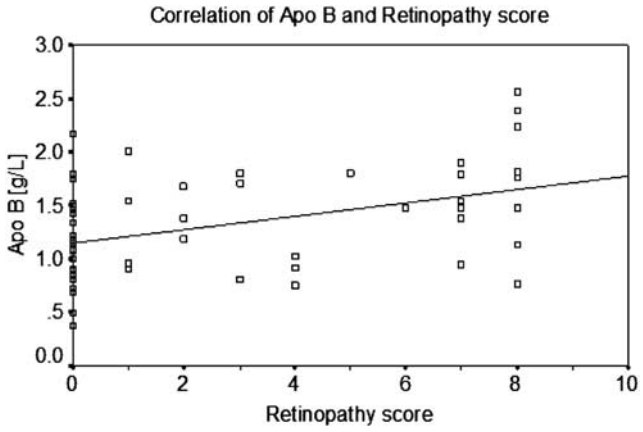
A/C, albumin/creatinine; Apo B, apolipoprotein B; MDRD, modification of diet in renal disease.
[a]Correlation is highly significant at the 0.01 level (two-tailed).
[b]Correlation is significant at the 0.05 level (two-tailed).

Table 2 Apolipoprotein B levels (mean ± SD) in groups of patients with no, single, or combined microvascular complications using a *t*-test

Groups	*N*	Apo B (g/l) (mean ± SD)	*t*-Test	*P*
No nephropathy	23	1.02 ± 0.341	4.427	<0.001
Nephropathy ± retinopathy	33	1.52 ± 0.469		
No complications	15	0.98 ± 0.361	2.596	<0.02
Nephropathy without retinopathy	10	1.38 ± 0.416		
No retinopathy	25	1.14 ± 0.427	2.600	<0.02
Retinopathy ± nephropathy	31	1.46 ± 0.491		
No nephropathy/no retinopathy	15	0.77 ± 0.361	2.141	<0.05
Nephropathy + retinopathy	18	1.26 ± 0.389		

Apo B, apolipoprotein B.

Figure 2



Correlation of apolipoprotein (Apo B) to the retinopathy score ($r=0.384$, $P=0.003$).

significant positive correlation was detected between the presence of maculopathy and the level of Apo B.

Discussion

Lipid abnormalities have long been associated with diabetic complications [6]. Yet, different studies have suggested that different lipid subgroups may be involved [3,7]. Furthermore, whether the relation between them is causal or a consequence has long been debated [5–7].

The use of Apo B as a marker of hyperlipidemia has been supported by many studies [8,9]. Apo B, as the structural protein of all proatherogenic lipoproteins, could provide the best estimate of the total number of atherogenic particles [10]. Plasma Apo B is an exact measure of the total number of VLDL and LDL particles; thus, total plasma Apo B is a reliable surrogate for the actual LDL particle number irrespective of its size [11]. This could explain why Apo B is elevated in diabetic patients even if the patient is normolipidemic [3].

We found that the Apo B level increases in direct proportion to the degree of diabetic nephropathy. The mean Apo B is correlated positively with incipient nephropathy than in those without nephropathy, and the mean Apo B increases even more in those with overt nephropathy than in patients with both normal and incipient nephropathy.

This is in agreement with the work of Jenkins *et al.* [8], who reported that high Apo B levels were associated with nephropathy in the form of a high albumin excretion rate. In addition, a case–control study from the EURODIAB by Chaturvedi *et al.* [7] showed that elevated Apo B was associated with albuminuria. Similarly, in a study from the DCCT/EDIC by Atchley *et al.* [12], Apo B was also increased in patients with overt nephropathy.

Bruno *et al.* [13] reported that Apo B *per se* is a predictor of progression to overt nephropathy, independent of the presence of microalbuminuria or hypertension. Furthermore, Weis *et al.* [14] reported that Apo B independently predicted the progression of albuminuria. Another study carried out by Hadjadj *et al.* [9] showed that the plasma concentration of Apo B was related to the stages of diabetic nephropathy.

There is now evidence that dyslipidemia can promote progression of renal damage in both diabetic and nondiabetic diseases [15]. Some studies showed that the plasma Apo B concentration is a significant predictive factor of progressive renal failure [2].

Microalbuminuria is often found in association with hyperlipidemia, especially in patients with diabetes and hypertension. Urinary protein loss may increase serum lipoprotein levels and lead to an increase in Apo B in such patients [16]. Alternatively, hyperlipidemia may contribute toward the progression of chronic kidney disease by a mechanism similar to atherogenesis.

Wagner *et al.* [11] reported that in normotriglyceridemic patients, Apo B identifies patients who are at risk better than non-high-density lipoprotein cholesterol. Its concentrations are a good estimate of the total mass of these particles, especially if LDL particles are predominantly small and dense. Walldius *et al.* [10] suggested that Apo B is a better predictor of cardiovascular events than LDL cholesterol. They also reported that Apo B, as the structural protein of all proatherogenic lipoproteins, provides the best estimate of the total number of atherogenic particles.

Thus, in type 2 diabetic patients, the total Apo B concentrations may provide information for a more complete lipid evaluation than LDL cholesterol alone. Furthermore, in our study, we excluded the effect of glycemic control (as our patients had HBA1c that was within the normal range) and also excluded patients on lipid-lowering agents.

Ozsoy *et al.* [2] reported that out of all the tested lipid parameters, only plasma Apo B concentration remained significant as a predictive factor of progressive renal failure.

Another study [17] found that higher A/C ratios were associated with higher intermediate density lipoprotein particle concentration and smaller mean LDL particle size. This was not discovered with the regular assays of LDL assessment. This occurs as regular assessments do not take into consideration the size and oxidation of the LDL particles.

In our study, we found a highly significant negative correlation between eGFR and Apo B. The same result was reported by Samuelsson *et al.* [18], who found that among lipoprotein variables, Apo B showed the strongest correlation with the decrease in GFR. Attman *et al.* [1] postulated that an increase in Apo B is accentuated with decreasing renal function.

In our study, we used eGFR, together with albuminuria, as an estimate of decreasing kidney function. De Boer and Steffes [19] showed that overt albuminuria does not always precede a significant loss of GFR in the setting of

diabetes (i.e. a decrease in eGFR may occur even in the absence of overt albuminuria) and that measurement of albuminuria alone does not fully capture the scope of early diabetic kidney disease. Hence, we have combined both methods of nephropathy assessment to correlate these data to Apo B levels.

We found that the mean level of Apo B increases in patients with nephropathy than in those without nephropathy. These results may also suggest that diabetic nephropathy including microalbuminuria plays an important role in the accumulation of atherogenic remnant lipoproteins in diabetic patients. Even in patients with nephropathy and without retinopathy, the Apo B level was still higher than that in those without any microvascular complications.

However, we also showed that the Apo B level was higher in the presence of both retinopathy and nephropathy than in those with only one microvascular complication. The presence of only one complication was associated with a still higher Apo B level than in patients without any microvascular complications. This is in agreement with Chaturvedi *et al.* [7], who postulated that both albuminuria and retinopathy were associated with quite marked disturbances in lipoproteins, especially Apo B, even in the early stages.

Furthermore, Fredrikson *et al.* [20] suggested that LDL oxidation is involved in the pathogenesis of diabetic retinopathy and that the autoantibodies detected against Apo B peptides could act as biomarkers for both microvascular and macrovascular complications in diabetes.

Reduced clearance and increased plasma levels of small dense LDL particles facilitate their entry into the arterial walls, causing renal and vascular damage [21]. In addition, chronic kidney disease results in the depletion of high-density lipoprotein-associated enzymes (serum paraoxonase and glutathione peroxidase 1) [6]. These abnormalities promote a predisposition to atherogenic adverse effects in affected individuals.

Dyslipidemia could accelerate progression of chronic kidney disease by several mechanisms. First, hyperlipidemia increases the rate at which reactive oxygen species are generated. It also decreases the production of nitric oxide and increases the production of angiotensin II, all resulting in renal injury and fibrosis [22]. Second, endoplasmic reticulum stress because of intracellular lipid deposition promotes cell damage [23].

Finally, lipid accumulation in the mesangium could lead to mesangial expansion. Takemura *et al.* [24] reported predominant deposition of Apo B-100 in the mesangial area in mesangial proliferative types of glomerulonephritis.

Our study found a significant correlation between the degree of retinopathy and Apo B. Van Leiden *et al.* [25] reported that retinopathy, hard exudates in particular, was related to elevated serum (LDL) cholesterol levels. This supports our findings as Apo B is a main component of LDL.

In addition, we found a significant correlation between Apo B and retinopathy grading, indicating that higher Apo B is accompanied by a higher grade of retinopathy. Most of the previous studies used LDL instead of Apo B and thus produced different outcomes [25–27].

Conclusion and summary

Apo B levels are correlated positively to the degree of nephropathy as well as to the degree of diabetic retinopathy, especially in the presence of maculopathy. The increase in Apo B is higher when both complications are present than when either is present alone or when neither is present.

Finally, our study suggests the use of Apo B-100 particle as a more sensitive and significant biomarker for early diabetic retinopathy and nephropathy. An additional advantage of Apo B over other microangiopathy markers is its correlation to both retinopathy and nephropathy. A larger number of patients are required to confirm our findings and also to assess the effect of early treatment of high levels of Apo B on the regression of nephropathy and retinopathy, especially in the early phases of diabetes.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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