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Original Research Article

The study of dyslipidemia and its correlation with nephropathy in diabetes mellitus type 2 patients

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ABSTRACT

Background: Diabetic nephropathy is one of the most severe diabetic microangiopathies. The aim of this study was to evaluate the lipid abnormalities associated with different stages of proteinuria in type 2 diabetic patients.
Methods: In this study 100 type 2 diabetic patients were subjected to detailed history, clinical examination, Serum lipid profile, urine albumin creatinine ratio and routine biochemical investigations.
Results: Out of 100 patients were included in study, 41 patients were normoabluminuric, 37 patients were microalbuminuric and 22 patients were overt proteinuric. Most common dyslipidemia found in study is increased triglyceride (43%) followed by increased LDL (28). On comparing normoalbuminuric to overt proteinuric, a positive correlation found in increased triglyceride (P value < 0.001) and increases LDL (P value <0.001).
Conclusions: Concluded that raised Triglyceride and LDL are associated with Diabetic Nephropathy.

Keywords: Albuminurea, Diabetes type 2, Dyslipedemia, Diabetic nephropathy, Proteinurea

INTRODUCTION

Diabetes mellitus is the most common metabolic disorder characterized by a series of hormone induced metabolic abnormalities and long-term complications.

Diabetic nephropathy is associated with an altered lipid profile characterized by elevated triglyceride rich lipoproteins, present even in the earlier stages of the renal disease. Although many experimental studies have demonstrated a significant deleterious role for dyslipidemia in both the initiation and progression of renal injury. A few prospective studies, mostly in type 2 diabetes, have suggested an independent role for serum cholesterol level in the subsequent development of incipient or overt diabetic nephropathy.

Diabetic nephropathy is a leading cause of death in many developed countries. Diabetic nephropathy carries its significance, as diabetes has become one of the most common cause of end stage renal disease (ESRD). Initial clinical evidence of nephropathy is the appearance of low but abnormal levels of albumin in the urine as "microalbuminuria" in which urinary albumin excretion rate (UAER) is between 20 µgm/min to 200 µgm/min or total urinary albumin/day between 30 mg to 300 mg/day or Spot collection 30 µg/mg creatinine to 299 µg/mg creatinine. If UAER is > 200 µmg/min or total urinary albumin/day is > 300 mg/day or Spot collection >299 µg/mg creatinine then it is known as "clinical albuminuria". Stage of microalbuminuria is also known as incipient nephropathy while stage of clinical albuminuria is known as stage of overt nephropathy. Once overt proteinuria develops, there is steady decline in GFR and approximately 50% of individuals reach ESRD in 7-10 years. The early pathologic changes and microalbuminuria are reversible with noramalisation of plasma glucose. But once overt nephropathy develops,

the pathologic changes are irreversible. 20-40% cases of Type 2 diabetes without specific interventions change from incipient to overt nephropathy shortly after diagnosis indicating its long asymptomatic period when tissue damage was relentlessly progressing, but only 20% cases of overt nephropathy with Type 2 diabetes develop ESRD.

The exact pathogenesis of microvascular complications in diabetes mellitus (DM) is unknown. Oxidative stress, activated renin-angiotensin system (RAS), hyperglycemia, advanced glycosylation end-products (AGE), and oxidized low-density lipoproteins are factor contributing to initiation and progression of endothelial inflammation, ultimately leading to diabetic vascular complications

Mechanisms of lipid-induced renal injury in the glomerulus

In human glomeruli, both mesangial and epithelial cells take up lipoproteins via specific receptors.[1-2]

Mesangial cells also express scavenger receptors which are involved in the preferential uptake of modified, glycosylated and oxidized LDL, as observed in diabetes.[3] Accumulation of modified LDL in the mesangium or in mesangial matrix has been reported to favor their uptake by infiltrated glomerular monocytes, leading in turn to the subsequent activation of these cells into macrophages.[4-5] This preferential phagocytosis of modified LDL by monocytes has been also reported to play a pivotal role in the formation of mesangial foam cells.[6]

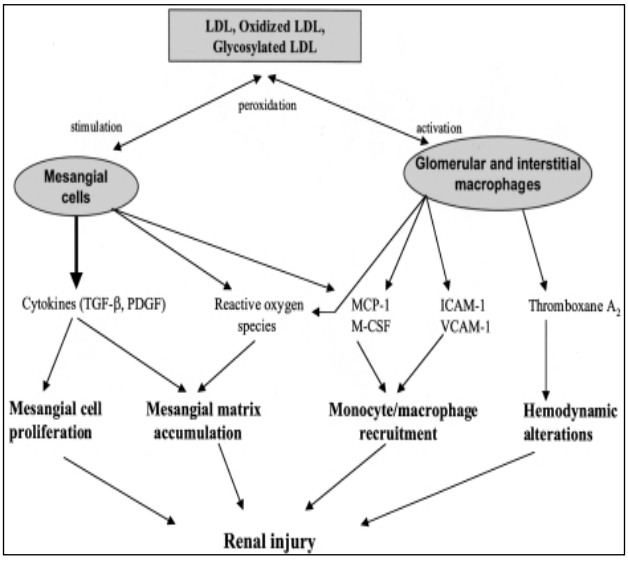

Figure 1: Schematic representation of possible pathophysiological mechanisms mediating lipid-induced renal injury.

As outlined in Figure 1, accumulated mesangial modified lipoproteins may influence the pathogenesis of glomerulosclerosis by different mechanisms: Exposure to oxidized lipoproteins has been reported to stimulate mesangial cell secretion of various chemotactic factors and adhesion molecules (M-CSF, ICAM-1, VCAM-1), enhancing the renal recruitment of macrophages.[7] These factors result in monocyte infiltration which has been reported to play a key role in the pathogenesis of glomerulosclerosis and tubular fibrosis, in particular in diabetic nephropathy.[8] These intra-mesangial recruited macrophages may in turn further oxidize LDL, creating a vicious self perpetuating cycle resulting in progressive renal injury (Figure 1). Renal activated macrophages have been shown to stimulate the release of reactive oxygen species and the expression of prosclerotic and proliferative cytokines such as transforming growth factor β1 (TGF- β1) and platelet-derived growth factor-AB (PDGF-AB). These cytokines stimulate the production of extra-cellular matrix proteins, promoting mesangial expansion as has been described in diabetic nephropathy.[9] In vitro studies have demonstrated that LDL and oxidized LDL stimulate TGF- β1 gene expression in both human glomerular mesangial and epithelial cells.[10,11] Therefore, TGF- β1 appears to be an important mediator of lipid-induced mesangial matrix expansion as well as playing a key role in the pathogenesis of diabetic nephropathy.[4,10-12]

Finally, the uptake of modified LDL by macrophages has been reported to stimulate eicosanoid synthesis including thromboxanes and leukotrienes, leading to potentially deleterious alterations in intra-glomerular hemodynamics.[6] In this regard, dietary cholesterol supplementation in animals has been shown to result in an increase in efferent arteriole resistance and a subsequent elevation in intra-glomerular pressure.[13] This effect may exacerbate glomerular injury in diabetic nephropathy (Figure 1).

In the tubulointerstitium

Tubulointerstitial injury has been clearly demonstrated over the last decade to play a pivotal role in the pathogenesis of diabetic nephropathy and to be an important predictor of renal dysfunction.[8] Animal studies have demonstrated a damaging effect of hyperlipidemia on the tubulointerstitium.[14] In these experimental studies, hyperlipidemia-induced chronic tubulointerstitial damage was associated with significant interstitial macrophage infiltration and a parallel increase in TGF- β1 gene expression in interstitial cells, suggesting a cytokine-mediated role for lipids in the development or aggravation of tubulointerstitial lesions.[7,14]

Furthermore, in proteinuric conditions such as overt diabetic nephropathy, it has been proposed from experimental in vivo studies that the tubular uptake and metabolism of the lipid component of filtered lipoproteins lead to local expression of chemokines and cytokines and promote interstitial inflammation.[15]

METHODS

A cross sectional study conducted on 100 diabetic patients were diagnosed case of Type 2 diabetes mellitus patients which were admitted and attend Medicine OPD in J. A. Group of Hospital.

Informed consent was taken from all the patients and each patient was subjected to detailed history and clinical examination, Serum lipid profile and Urine albumin creatinine ratio and routine investigations are done. Patients with urinary tract infection, obstructive uropathy and on statins were excluded.

Table 1: Cases of diabetes diagnosed based on the ADA-WHO diagnostic criteria for diabetes.

Stage	Fasting plasma glucose test (FPG)	Casual plasma glucose test	Oral glucose tolerance test (OGTT)
Diabetes	FPG greater than or equal to 126 mg%	Casual plasma glucose greater than or equal to 200 mg% plus symptoms	Two-hour plasma glucose (2hPG) greater than or equal to 200 mg%
Impaired glucose homeostasis	Impaired fasting glucose (IFG) = FPG greater than or equal to 110 and less than 126 mg%		Impaired Glucose Tolerance (IGT) = 2h PG greater than or equal to 140 mg% and less than 200 mg%
Normal	FPG less than 110 mg%		

Urinary albumin creatinine ratio calculated by

- Urinari albumin: Immunoturbidimetric assay.
- Urinari creatinine: Jaffé rate reaction assay.

Urinary albuminuria classified by

normoabuminurea <30, microalbuminurea 30 - 300, overt proteinurea > 300 µg/mg creatinine (Adapted from ADA).[16]

Lipid values were classified according to NCEP ATP III Guidelines: Total Cholesterol > 200 mg%, Triglyceride > 150 mg%, LDL >100 mg%, HDL < 40 mg%.[17]

Stastical analysis

Data analysis was done by software EPICAL and p value are measured in all statistics by Chi square (x^2) test and ANOVA test. P value <0.05 was considered significant.

RESULTS

In this study most common lipid abnormality in ↑TG level which is 43%, out of which males were 62.79% (n=27) and 37.20% were (n=16) female, followed by ↑LDL which is 28%, of which males were 50% (n=14) and 50% were (n=14) female Table 2.

Table 2: Lipid profile distribution in cases.

Parameters	Male		Female		Total
	No.	%	No.	%	
↑TC	8	13.33	10	23.25	18
↑TG	27	45.00	16	37.20	43
↑LDL	14	23.33	14	32.58	28
↓HDL	11	18.33	3	6.97	14
Total	**60**	**100**	**43**	**100**	**103**

Table 3: Gender wise distribution of different ranges proteinuria in cases.

	Normo-albuminuria		Micro-albuminuria		Overt proteinuria		Total
	No.	%	No.	%	No.	%	
Male	27	65.85	22	59.45	13	59.09	62
Female	14	34.14	15	40.54	9	40.90	38
Total	**41**	**100**	**37**	**100**	**22**	**100**	**100**

Table 4: Correlation of lipid profile in patients with different ranges of proteinuria.

Para-meters	Normo-albuminuria		Micro-albuminuria		Overt proteinuria		Total	p value
	No.	%	No.	%	No.	%		
↑TC	6	21.42	4	15.38	8	16.32	18	>0.05
↑TG	10	35.71	13	50.00	20	40.81	43	<0.001*
↑LDL	7	25.00	6	23.07	15	30.61	28	<0.001*
↓HDL	5	17.85	3	11.53	6	12.24	14	>0.05
Total	28	100	26	100	49	100	103	

*Statistically significance.

Females patients were more ↑TG and ↑ TC as compare to males while ↑LDL were equally distributed between male and females. Of the total 100 diabetic patients included in this study 62 of them were male and 38 were female. Maximally 41% patients were normoalbuminuric Followed by 31% microalbuminuric, followed by 22% patients had overt protienuric. Out of 41 normoalbuminuric patients, 65.85% patients were males (n=27) and 31.14% patients were females (n=14). Out of 31 microalbuminuric patients 59.45% patients were males (n=22) and 40.54% patients were females (n=15). Out of 22 overt protienuric patients, 59.09% patients were males (n=13) and 40.90% patients were females (n=9) (Table 3).

Above Table 4 shows that all forms of dysilipidemia, majority of patients were overt proteinuric but on statistical analysis positive correlation was obtained only for ↑TG (P value <0.001) and ↑LDL (P value <0.001).

DISCUSSION

In present era diabetes is the most common endocrine disorder which prevalence is 6.5% of entire population worldwide is still on rise owing to the interaction of various host and changing environmental factors. India is the world capital of diabetes. Dyslipidemia has been hypothesizing to play an important role in progression of proteinurea in diabetes nephropathy.

In present study total 100 diabetic patients were included, out of which 41 patients were normoalbuminuric, 37 patients were microalbuminuric and 22 patients were overt proteinuric. Of the total 100 patients, maximally 41% patients were normoalbuminuri Followed by 31% microalbuminuric, followed by 22% patients had overt protienuric Table 3.

Dyslipidemia and proteinuria

In present study all forms of dysilipidemia, majority of patients were overt proteinuric but on statical analysis positive correlation was obtained only for ↑TG (P value <0.001) and ↑LDL (P value <0.001). Which is highly significant. Henri Afghahi et al also found development of albuminuria or renal impairment in diabetes patients independently associated with ↑TG level (P value <0.02) and ↓HDL (P value < 0.05). Which is similar to our study.[18]

Smulders YM, also found similar to our study that serum triglyceride (TG) concentration correlated with progression of microalbuminuria.[19]

Yang X et al was found in their study, that macroalbuminuria associated with ↑TC and ↑LDL levels.[20]

Mordchai Ravid et al, found that ↑TC ↑LDL in ↓HDL associated with decreased renal function and with increased albuminuria.[21]

Above studies differed from our study that our present sample study mostly north Indian, main staple diet is vegetarian food where as other study conducted in the respective population mostly consume food which is reach in trans and saturated fat thus the total cholesterol element is on the higher side where as in our study increased TG and LDL mainly abnormal due to synthesis abnormality in Diabetes.

Patel ML et al, also found statically significant (P value <0.001) ↑TG, ↑LDL level when compare to normoalbuminuric to macroalbuminuric patients. Which is similar to our study.[22] Jha P et al, found similar to our study, that all diabetic subject exhibited mark lipid abnormality characteristics by ↑TG which were significant two diabetic group with micro and macroalbuminuria when compare to normoalbuminuria patients.[23]

Retnakaran R et al, found similar to this study that risk factor for development of proteinuria were ↑TG, ↑LDL levels. Which is similar to our study.[24]

Hasslacher C et al, also found similar to our study, ↑TG level have been shows to be risk factor for more rapid progression of nephropathy in diabetes type to patients which overt proteinuric.[25]

CONCLUSION

The study entitled “the study of dyslipidemia and its correlation with nephropathy in diabetes mellitus type 2

patients'' is of cross sectional study done in department of medicine G.R. Medical College Gwalior Madhya Pradesh for a sample of 100 patients of type 2 Diabetes mellitus (excluding the cases of UTI, obstructive uropathy and taking statin) revealed that dyslipidemia of increased Triglyceride and LDL where is the statistically significant found correlation with diabetic nephropathy.

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Ethical approval: The study was approved by the institutional ethics committee

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