

Research Article

Association between Postsprandial Triglyceride Levels and Urinary Albumin Excretion in Type II Diabetic Subjects - A Case-Control Study in North Indian Population

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Abstract

Aim: To evaluate and correlate 2-hour postprandial lipid profile and urine albumin excretion in patients with type II Diabetes Mellitus.

Method: This case-control study included 148 subjects with Type II Diabetes mellitus and 96 age and gender matched healthy controls. Fasting and 2-hour postprandial blood samples were collected from all subjects and analyzed for plasma glucose, serum insulin, serum cholesterol, triglycerides and high-density lipoproteins. In addition fasting samples were analyzed for glycated haemoglobin (HbA1c) and kidney function tests. Percentage retention of triglyceride in plasma at the end of two hours and HOMA-IR as a measure of Insulin resistance was calculated. Spot urine sample collected from all subjects within two hours waiting period was analyzed for urine albumin/ creatinine ratio. Statistical evaluation of data was done on SPSS and Medcalc online software.

Result: Plasma glucose, insulin and HbA1c levels were significantly higher in diabetic subjects as compared to control group ($p < 0.01$). Serum cholesterol and HDL levels did not have a significant difference in fasting and postprandial state in both groups. The difference in triglyceride levels between study and control group was insignificant in fasting state ($p = 0.051$) but highly significant in postprandial state ($p < 0.001$). Percentage triglyceride retention in plasma after 2 hours was significantly higher in diabetic patients [$16.43 \pm 28.25\%$] as compared to control group [$2.56 \pm 19.17\%$] ($p = 0.002$). Postprandial serum triglyceride levels in diabetic subjects showed a highly significant positive correlation with urinary albumin excretion in these subjects ($r = 0.444$, $p < 0.001$). Odds ratio for presence of hypertriglyceridemia in patients with microalbuminuria was 18.667 (95% CI of 6.64 to 52.45, z-static-5.55, $P < 0.0001$).

Conclusion: Diabetic subjects excreting micro-albumin in urine have exaggerated postprandial lipidemia as compared to patients with no micro-albumin excretion and normal subjects. This may be regarded as one of the mechanisms by which microalbuminuria in diabetic patients contributes to increased cardiovascular risk.

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Introduction

Diabetes mellitus (DM) is a global health issue affecting adults and children in both developed and developing countries. It has been predicted to be the seventh leading cause of death by 2030^[1]. According to the World Health Organization, approximately 347 million people worldwide and over 90% of diabetics currently have type 2 DM (T2DM)^[1]. People with diabetes have a 4-fold-greater risk of suffering from cardiovascular disease (CVD) than people without diabetes after controlling for traditional risk factors such as age, obesity, tobacco use, dyslipidemia, and hypertension^[2,3]. CVD is also one of the leading causes of death (approximately 70%) in people with type 2 diabetes^[4,5]. Approximately 80% of people with diabetes live in low and middle-income countries^[1]. According to the Indian Council of Medical Research-Indian Diabetes study (ICMR-IN-

DIAB), India currently has 62.4 million people with diabetes^[6] which is expected to increase further to over 100 million by 2030^[7]. While T2DM predominantly affects older individuals in developed countries, it is known to affect younger population in the prime of their working lives in developing countries like India. This poses a greater threat to the health of these individuals^[6,8].

Microalbuminuria (MA) is a common and well established risk factor for macro vascular diseases in patients with T2DM^[9,10]. Dyslipidemia is common in T2DM and is characterized by high levels of fasting triglycerides (TG), low HDL cholesterol levels, and predominance of small, dense LDL cholesterol particles^[11,12]. Epidemiological data suggest that high plasma TG levels, both in fasting and postprandial state are associated with cardiovascular diseases in patients with

diabetes^[13,14]. Majority of patients with T2DM show high and prolonged postprandial dyslipidemia^[15-17]. Some recent evidence suggests that postprandial plasma triglyceride levels predict future myocardial infarction better than fasting triglyceride levels^[18], therefore postprandial triglyceride levels deserve more attention in assessment of heart disease risk^[19,20]. It is also known that there exists a population of patients whose fasting glucose and triglyceride levels are within normal range, but they present with postprandial hyperglycaemia and hypertriglyceridemia. This has led to recognition of both postprandial hyperglycaemia and dyslipidemia as risk factors for cardiovascular disease^[21]. Deranged lipid pattern in postprandial hyperglycaemic condition can be explained by the single concept of “postprandial metabolic disorder”.

The association between postprandial metabolic disorder and urinary albumin excretion has not been evaluated, though both have been independently linked to increased cardiovascular risk in T2DM patients. Hence this study was planned to evaluate the extent of postprandial dyslipidemia and urine albumin excretion in T2DM patients and to find their correlation in a hospital set up.

Method

This case-control study was carried out in a tertiary care hospital in an urban setup of North India. The study was approved by Institutional Ethical Committee and included 148 subjects with Type II Diabetes Mellitus in the age group of 40-50 years and 96 age and gender matched healthy controls. Brief clinical history was taken from all subjects regarding duration of disease or presence of any complications of diabetes. Urine sample was screened for presence of albumin using dipstick to rule out overt nephropathy. Only those patients who had negative albumin or traces were included in the study.

Overnight fasting and 2-hour postprandial blood samples were collected from all subjects after written and informed consent. The samples were collected in Sodium Fluoride –EDTA tubes for plasma sugar, EDTA tubes for glycated haemoglobin (HbA1c) and silicon coated tubes with separator gel for serum insulin, serum cholesterol, serum triglycerides, high-density lipoproteins (HDL-C) and Kidney function tests (Serum urea, creatinine and uric acid levels). Spot urine sample collected in a clean, dry and sterile container within two hours waiting period was analyzed for urine albumin/creatinine ratio.

Urine albumin concentration and HbA1c were estimated by immuno-turbidimetric method. Kidney function tests, lipid profile and plasma sugar were measured on AU 480 fully automated Biochemistry Analyzer using Kits, calibrators and controls from Beckman Coulter. Urine albumin/creatinine ratio (A/ Cr) (mg of albumin/gram of creatinine) was calculated. Urine A/Cr ratio ≥ 30 mg/g of creatinine was considered as presence of microalbuminuria in patients and controls.

Serum Insulin was estimated by electro-chemiluminescence method.

Percentage retention of triglycerides in plasma at end of two hours was estimated by using the formula

$$\frac{((\text{postprandial TG}-\text{fasting TG}) \times 100)}{(\text{fasting TG})}$$

In each subject, presence of Insulin resistance was estimated by HOMA-IR according to method described by Matthews et al^[22], using the formula:

$$\frac{(\text{fasting plasma glucose (FPG)}(\text{mg/dL}) \times \text{fasting serum insulin (FSI)} (\text{mU/L}))}{405}$$

Low HOMA-IR values indicate high insulin sensitivity, whereas high HOMA-IR values indicate low insulin sensitivity (insulin resistance).

Another score of Insulin Sensitivity – Quantitative Insulin Sensitivity Check Index (QUICKI) was calculated in each subject. QUICKI was calculated from fasting plasma glucose and fasting insulin levels according to the report by Katz et al.^[23] using the following formula

$$\text{QUICKI} = 1/(\log [\text{FSI in mU/L}] + \log [\text{FPG in mg/dL}]).$$

All the data was analyzed on SPSS for windows version 18.0(SPSS Inc., Chicago, IL, USA). Data is presented as Mean \pm Standard Deviation. For categorical variables, ANOVA was applied. For continuous variables Student’s t-test was applied. The difference between groups was compared by independent sample t test or Mann–Whitney test for continuous variables. Spearman’s rank correlation was applied for association between continuous variables. Linear simple or multiple regression analysis was performed for analysis of association among microalbuminuria and clinical covariates, including QUICKI, HOMA-IR, Odds ratio and 95% confidence interval were calculated using Med Calc Software online for determining the significance of hypertriglyceridemia in patients with microalbuminuria. A two-tailed p value < 0.05 was considered statistically significant.

Result

The mean age group of diabetic patients was 45.82 ± 2.13 years and that of control group was 46.0 ± 1.93 years. The difference was not found to be statistically significant.

Biomarkers in fasting state

Fasting plasma sugar and Insulin values were found to be significantly raised in diabetic subjects as compared to normal subjects (Table1). Fasting cholesterol values were comparable in both the groups, however fasting triglycerides were higher in diabetic patients, though the results were not found to be statistically significant ($p=0.051$). Difference in serum HDL was not found to be statistically significant in two groups.

Table 1: Differences in diabetic and Insulin resistance markers between control group and diabetic patients.

S. No.	Test Name	Control Group (n=96)	Diabetic patients (n=148)	Level of significant difference
1	Fasting plasma Glucose (mg/dL)	89.8 ± 11.87	168.5 ± 65.9	P<0.001
2	Postprandial Plasma Glucose (mg/dL)	113.9 ± 3.65	245.6 ± 71.8	P<0.001
3	Fasting Cholesterol (mg/dL)	137.4 ± 30.5	143.6 ± 37.9	P=0.321
4.	Postprandial Cholesterol (mg/dL)	138.4 ± 30.04	148.1± 39.6	P=0.128
5.	Fasting Tri-glycerides (mg/dL)	125.6 ± 65.75	196.8 ± 102.3	P=0.051
6.	Postprandial Tri-glycerides (mg/dL)	129.7 ± 57.05	265.9 ± 167.4	P< 0.001
7	Fasting Serum HDL (mg/dL)	40.80 ± 6.5	40.67 ± 5.3	P=0.543
8.	Postprandial serum HDL (mg/dL)	40.38 ± 6.85	41.8 ± 6.3	P=0.228
9.	Fasting Insulin (mIU/L)	3.19 ± 1.19	7.05 ± 6.2	P<0.001
10.	Postprandial Insulin (mIU/L)	8.08 ± 5.2	14.28 ± 14.1	P=0.003
11	HbA1c (%)	5.6 ± 2.05	6.7 ± 5.9	P=0.006
12.	Triglyceride retention (2 Hr) (%)	2.56 ± 19.17	16.43 ± 28.25	P=0.002
13.	Urine A/Cr (mg/g of Creatinine)	7.93 ± 4.2	42.1 ± 37.2	P<0.001
14	HOMA-IR	0.7 ± 0.4	2.93 ± 2.8	P<0.001
15	QUICKI	0.42 ± 0.03	0.34 ± 0.04	P<0.001

HbA1c- Haemoglobin A1c fraction; A/Cr – Albumin/ Creatinine ratio of spot urine sample; HOMA-IR – Homeostasis Model Assessment- Insulin Resistance (surrogate marker for Insulin resistance); QUICKI- Quantitative Insulin Sensitivity Check Index [For details, refer to text]

Plasma HbA1c values and urine albumin excretion were also significantly higher in diabetic patients as compared to the control group (p-value 0.006 and <0.001 respectively) (Table1). Kidney function tests (Serum urea, creatinine, uric acid) were comparable in both the groups.

Biomarkers in postprandial state

Plasma sugar and serum Insulin values were significantly higher in postprandial state in both the groups (table 2 and 3). Postprandial serum total cholesterol was not found to be significantly different from fasting levels in both the groups. Postprandial serum triglycerides were comparable to fasting levels in control group (Table 2) but significantly higher in diabetic patients (Table 3).

Postprandial serum triglycerides were very significantly raised in diabetic patients as compared to control group (265.9 ± 16.74 mg/dl vs 129.7 ± 8.07 mg/dl, p=0.001). Postprandial Serum HDL was comparable in two groups.

Table 2: Comparison of fasting and postprandial metabolic parameters in control group (n=96)

S. No.	Test Name	Fasting state	Postprandial state	Level of significant difference	95% CI of mean difference
1	Plasma Glucose (mg/dL)	89.8 ± 11.87	113.9 ± 25.80	P<0.001	(17.63, 30.53)
2	Serum Cholesterol (mg/dL)	137.4 ± 30.5	138.4 ± 30.04	P=0.620	(-4.93, 2.97)
3	Serum Tri-glycerides (mg/dL)	125.6 ± 65.75	129.7 ± 57.05	P=0.847	(-8.03, 9.75)
4.	Serum HDL (mg/dL)	40.80 ± 6.50	40.38 ± 6.85	P=0.927	(-1.03, 2.01)
5.	Serum Insulin (mIU/L)	3.19 ± 1.90	8.08 ± 5.2	P<0.001	(3.48, 6.29)

Table 3: Comparison of fasting and postprandial metabolic parameters in diabetic group (n=148)

S. No.	Test Name	Fasting state	Postprandial state	Level of significant difference	95% CI of mean difference
1	Plasma Glucose (mg/dL)	168.5 ± 65.9	245.6 ± 71.8	P<0.001	(67.98, 86.16)
2	Serum Cholesterol (mg/dL)	143.6 ± 37.9	148.1± 39.6	P=0.012	(1.01, 8.09)
3	Serum Tri-glycerides (mg/dL)	196.8 ± 102.3	265.9 ± 167.4	P<0.001	(36.5, 106.8)
4.	Serum HDL (mg/dL)	40.67 ± 5.3	41.8 ± 6.3	P=0.114	(0.39, 1.97)
5.	Serum Insulin (mIU/L)	7.05 ± 6.2	14.28 ± 14.1	P<0.001	(4.74, 9.71)

Surrogate marker of insulin resistance (HOMA-IR) was significantly raised and for Insulin sensitivity (QUICKI), a significant decrease was observed in diabetic patients as compared to control group (Table 1).

Percentage retention of triglycerides in plasma at end of 2 hours was calculated as a quantitative measure of clearance of triglycerides from patient's plasma. Mean retention of triglycerides in diabetic patients was 16.43 ± 28.25% as compared to 2.56 ± 19.17% in normal subjects (p=0.002). Urine albumin excretion was significantly higher in diabetic patients (42.1 ± 37.2 mg/g of creatinine) as compared to the control subjects (7.93 ± 4.2 mg/g of creatinine) (p<0.001).

Comparison of lipid profile in diabetic patients with and without microalbumin excretion

Diabetic patients were further divided into two groups- Patients with microalbuminuria (n=63) (Urine A/Cr ≥ 30 mg/gram of creatinine), and patients without microalbuminuria (n=85) (Urine A/Cr < 30 mg/gram of creatinine). Fasting and postprandial cholesterol and triglyceride levels were significantly higher in diabetic patients with microalbuminuria as compared to those with lower levels of albumin excretion (Table 4). However, no significant difference was observed in HDL levels in both the groups.

Table 4: Comparison of biochemical parameters in diabetic patients with normal albumin excretion/ microalbumin excretion

S. No.	Test Name	Diabetic patients with Albumin excretion <30 mg/g (n=85)	Diabetic patients with Albumin excretion ≥30 mg/g (n=63)	Level of significant difference	95% CI of mean difference
1	Fasting serum cholesterol (mg/dL)	133.2 ± 28.5	154.7 ± 29.3	P= 0.025	(0.91, 7.56)
2	Post prandial serum Cholesterol (mg/dL)	135.8 ± 26.7	160.8 ± 30.5	P=0.010	(3.01, 9.63)
3	Fasting serum triglycerides (mg/dL)	149.4 ± 49.2	268.1 ± 119.7	P<0.001	(65.89, 169.2)
4	Postprandial serum triglycerides (mg/dL)	167.9 ± 55.6	314.38 ± 132.9	P<0.001	(96.24, 206.51)
5	Fasting serum HDL (mg/dL)	40.35 ± 4.3	40.62 ± 4.3	P=0.436	(0.45, 1.32)
6.	Postprandial serum HDL (mg/dL)	40.47 ± 5.1	41.9 ± 5.9	P=0.634	(0.61, 2.01)
7	Urine Alb/ Creat Ratio (mg/g)	16.59 ± 7.36	82.07± 71.6	P<0.001	(35.21, 189.3)

Correlation of Biochemical markers with urine A/ Cr ratio and HbA1c values

Fasting and postprandial sugar, insulin, lipid profile and kidney function tests were correlated with urine albumin excretion and HbA1c values in diabetic subjects as shown in Table 5. Postprandial sugar levels showed a significant positive correlation and serum Insulin levels showed a significant negative correlation with HbA1c levels. Serum postprandial triglyceride levels showed a significant positive correlation with urine albumin/creatinine ratio ($r=0.444$, $p<0.001$) in diabetic patients. When the diabetic patients were divided into two groups based on their urine /Cr, the observed correlation was higher in patients with $A/Cr \geq 30$ mg/g ($R=0.603$, $p<0.001$) than patients with $A/Cr < 30$ mg/g ($R=0.230$, $p=0.02$). Thus presence of albumin in urine correlated with the presence of hypertriglyceridemia in diabetic patients and the correlation was found to be more significant in postprandial state as compared to fasting state.

Table 5: Correlation of biochemical parameters (associated with renal and cardiovascular risk with urinary Albumin- Creatinine ratio (A/ Cr) and Glycated haemoglobin (HbA1c) values in diabetic patients

S.No.	Test Name	With A/Cr values	With HbA1c values
1	Fasting Plasma Sugar	R=0.135, p= 0.180	R=0.217, p=0.030*
2	Postprandial Plasma Sugar	R=0.022, p= 0.846	R=0.210, p=0.036*
3.	Fasting Serum Cholesterol	R=0.116, p=0.251	R=0.011, p=0.911
4.	Postprandial Serum Cholesterol	R=0.04, p=0.691	R=0.057, p= 0.571
5.	Fasting Triglycerides (with normal albumin excretion)	R= 0.148, p=0.369	R=-0.017, p=0.868
6.	Fasting Triglycerides (with A/Cr ≥ 30mg/g creatinine)	R=0.336, p<0.001*	R= 0.110, P=0.276
7	Postprandial Tri-glycerides (with normal albumin excretion)	R=0.230, p=0.02*	R= 0.108, p=0.290
8.	Postprandial Tri-glycerides (with A/Cr ≥ 30mg/g)	R= 0.603, p<0.001*	R= 0.028, p=0.786
9.	Postprandial Insulin Values	R=-0.022, p= 0.83	R=-0.221, p=0.027*
10.	Serum Urea	R=0.234, p= 0.019*	R= -0.106, p= 0.293
11.	Serum creatinine	R= 0.263, p=0.008*	R=-0.107, p= 0.288
12.	Serum Uric Acid	R=0.247, p=0.013*	R= 0.010, p=0.918

* $p<0.05$ (Significant correlation)

Odds ratio for the presence of hypertriglyceridemia in patients having microalbuminuria was found to be 18.667 (95% CI of 6.64 to 52.45, z-static-5.55, $P<0.0001$).

Discussion

Hyperlipidemia is a metabolic abnormality frequently associated with diabetes mellitus. Its prevalence is variable, depending on the type and severity of diabetes, glycemic control, nutritional status, age and other factors. The most characteristic lipid abnormality in diabetics is hypertriglyceridemia, with or without associated increase in plasma cholesterol^[24].

In the present study, fasting and postprandial sugar and insulin values were significantly raised in diabetic subjects as compared to controls. These observations can be explained on the basis of aetiology of the disease and the fact that most of T2DM subjects are insulin resistant. In the present study, mean HOMA-IR in control group was found to be significantly less and Insulin sensitivity marker (QUICKI) was significantly higher than in diabetic subjects. These findings can be explained with the fact that Type II diabetes is usually a sequelae to insulin resistance^[25].

In present study, there was no significant difference in serum cholesterol levels and HDL in fasting and postprandial state in normal subjects and diabetic subjects. However, all diabetic patients showed significantly raised post prandial triglyceride levels as compared to the fasting levels. The findings of present study are similar to the findings of Tentolouris et al.^[26] where 2-hour postprandial cholesterol levels were not found to be significantly different from fasting levels in diabet-

ic subjects excreting micro-albumin in urine. The findings of present study are in contrast to the findings of Rathore et al.^[24] where a significant postprandial increase was observed in serum cholesterol and triglyceride levels in diabetic patients.

In this study, 63 diabetic patients were diagnosed to have microalbuminuria and rest of the 85 patients had urine albumin excretion less than 30mg/g creatinine. Fasting and postprandial serum cholesterol and triglyceride levels were significantly higher in diabetic subjects with microalbuminuria as compared to those without microalbuminuria (Table 4).

Percentage retention of triglycerides in plasma at the end of 2 hours was significantly higher in diabetic patients ($16.43 \pm 28.25\%$) as compared to ($2.56 \pm 19.17\%$) in normal subjects ($p=0.002$). Previous studies have shown that both hepatically derived and intestinally absorbed triglycerides contribute to exaggerated postprandial lipidemia in Type II diabetic subjects. None of the studies till date have evaluated post-prandial lipidemia on a numerical scale. This study utilized the formula for the first time for calculation and comparison of percentage retention of triglycerides in study and control group.

Lefebvre (1998) reviewed that increased postprandial glucose levels and high postprandial triglyceride levels and triglyceride rich lipoproteins may damage vascular endothelial cells and contribute to an increased risk for CVD^[27].

Mean HbA1c levels and urine A/Cr was significantly higher in diabetic patients as compared to control subjects. Both of these indicators are considered as predictors of micro vascular complications in diabetes and poor cardiovascular outcome in T2DM subjects^[28-30]. The data presented in table 5 shows the correlation of HbA1c values and urine A/Cr with serum lipid profile, serum insulin, and plasma sugar and kidney functions test. Urine A/Cr was found to have highly significant positive correlation with postprandial triglyceride levels ($r=0.444$, $p<0.001$). When the diabetic patients were segregated into two groups based on their urine A/Cr ratio, the diabetic patients with microalbuminuria demonstrated highly significant correlation between serum triglycerides and Urine A/Cr ratio both in fasting and postprandial state. In diabetic patients a significant positive correlation between serum triglycerides and Urine A/Cr was observed only in postprandial state. The Odds Ratio for the occurrence of hypertriglyceridemia in presence of microalbuminuria was also found to be highly significant ($p<0.0001$) in this study. Another study carried out on 64 diabetic subjects with and without microalbuminuria also shows a significant positive correlation between micro-albumin excretion in urine and postprandial triglyceride values^[26].

Lipoprotein lipase is the key enzyme in the postprandial processing of triglycerides derived from diet as well liver^[26]. At high plasma TG levels, LPL actions are saturated, leading to defects in the clearance of both hepatically and intestinally derived TG-rich lipoproteins^[26,31]. Deckert et al. in 1989 have suggested that presence of micro-albumin in urine of patients with Type II diabetes may indicate widespread vascular damage and hence decreased lipoprotein lipase activity^[32]. Some of the animal based studies indicate that postprandial lipidemia in dia-

betic subjects may correlate with their insulin resistant states due to increased production of apo-B48 in the intestines^[33], but in the present study, no correlation was observed between HOMA-IR and post-prandial triglyceride levels.

In clinical practice, lipid profile is measured only in the fasting state. However, considering the normal eating habits of North Indian urban population, a significant part of the day is spent by an individual in postprandial state. The traditional lipid profile test often requires 8-12 hour fasting samples. Some of the diabetic patients cannot remain fasting for such a long period, hence taking 2-hour postprandial samples from diabetic patients for serum triglycerides may be considered as a better option not only due to the ease of obtaining sample but also because it can be more useful for CVD risk stratification in diabetic patients. The detection rate of hypertriglyceridemia in diabetic patients will improve if such a strategy is adopted. Few recent studies advocate multiple readings for accurate classification of postprandial dyslipidemia. However, the researchers in present study have shown that even a single postprandial measurement of serum triglyceride will provide information about increased cardiovascular risk in diabetic patients.

Till date, evaluation of post prandial dyslipidemia has been carried out in research settings only. The novelty of this study is that the diabetic patients were evaluated during a routine follow up visit in a clinical set up and their postprandial lipid profile values were compared to non-diabetic control subjects and correlated with urinary albumin excretion.

Conclusions

Irrespective of underlying mechanisms, the results of this study demonstrate that albumin excretion in type II diabetic subjects is associated with enhanced postprandial triglyceridemia. Substantial evidence suggests that postprandial triglyceride rich lipoproteins are atherogenic, the findings of this study are noteworthy and may explain in part the excess cardiovascular disease risk in diabetic patients excreting micro-albumin in urine. Thus, there is a need to address the postprandial metabolic disorder in diabetic patients to reduce their cardiovascular disease risk.

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