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DIAGNOSTIC UTILITY OF SERUM LIPID PROFILE AND URINARY MICROALBUMIN FOR ASSESSING CARDIO METABOLIC RISK AND EARLY DIABETIC NEPHROPATHY IN TYPE 2 DIABETES MELLITUS

Namala Venkatesh[1], K.V.N. Rajeswari[2], B. Vikram[3], Jahnavi Alwala[4*]

[1]Department of Biochemistry, Chaitanya Deemed to be University, Moinabad, Hyderabad, Telangana-500075, India. ORCID ID: 0009-0001-2844-8902, namalavenkatesh569@gmail.com
[2]Department of Biochemistry, Chaitanya Deemed to be University, Moinabad, Hyderabad, Telangana-500075, India. ORCID ID: 0009-0002-6221-7566, kvnrajeswari@gmail.com
[3]Department of Biochemistry, Chaitanya Deemed to be University, Moinabad, Hyderabad, Telangana-500075, India. ORCID ID: 0000-0002-0898-3051, vikramb2662@gmail.com
[4*]Department of Biochemistry, Chaitanya Deemed to be University, Moinabad, Hyderabad, Telangana-500075, India. ORCID ID: 0000-0002-7796-8840, jahnavichandu.enjapuri@gmail.com
*Corresponding Author: Jahnavi Alwala, Email ID: jahnavichandu.enjapuri@gmail.com

ABSTRACT
Diabetes mellitus is a chronic metabolic disease interpretive by steady hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. Dyslipidemia is a common metabolic abnormality associated with T2DM and significantly subsides the development of atherosclerotic cardiovascular disease, leading to the cause of morbidity and mortality among diabetic patients. Evaluation of serum lipid profile and urine microalbumin provides useful information regarding early detection of cardio metabolic risk and diabetic nephropathy. The present study aimed to evaluate serum lipid profile and urine microalbumin as biomarkers in patients with Type 2 Diabetes mellitus by comparing lipid and micro albumin parameters between diabetic patients and healthy controls for the early assessment of cardio metabolic risks and diabetic nephropathy. A total of 600 participants were subjected into two categories Diabetes patients (n=300) and controls (n=300) and gender wise into three categories based on age. Overnight Fasting venous blood samples were collected for characterization of serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C) and also urine albumin were estimated by Cholesterol Oxidase–Peroxidase (CHOD–POD) method and microalbumin by Immuno Turbidimetic method using Erba Chem7 Semi auto analyzer. Statistical analysis was performed using Mann–Whitney U test and micro albumin prevalence was assessed by using chi-square test. This study demonstrates the significant changes in serum lipid profile cases with Type 2 Diabetes mellitus compared with controls. Elevated TC, TG, LDL-C, and VLDL-C, together with reduced HDL-C and urine albumin serve as valuable biomarkers for the early assessment and clinical management of metabolic dysfunction, cardiovascular and renal risk in T2DM.

KEYWORDS: Type 2 Diabetes mellitus, Serum lipid profile, Urinary microalbumin, Cardio metabolic Risk, Early Diabetic Nephropathy, Biomarkers.

INTRODUCTION
Diabetes mellitus is a metabolic disorder combined with chronic hyperglycaemia which results in complete or partial decline in insulin secretion or biological action of insulin [1].Type 2 Diabetes (T2D) or Diabetes mellitus (DM) is an incommunicable chronic disease with high cause of the morbidity and mortality leading to severe outcomes such as kidney failure, cardiovascular disease (CVD), and diabetic retinopathy [2, 3].
Insulin resistance (IR) is a brainstorm aspect to play a key role in the pathogenesis of type 2 Diabetes [4] along with its key role in microvascular complications. One of the overwhelming complications of Diabetes is diabetic nephropathy which leads to the cause for End Stage Renal Disease (ESRD) and cardiovascular mortality [5] and IR can be a prognostic marker of diabetic nephropathy. Earlier studies have shown that insulin resistance is present in patients with mild renal disease [6, 7]. Diminished insulin sensitivity has shown to associate with reduce renal function also in non diabetic individuals [8, 9]. Diabetic nephropathy (DN) is the prominent cause of chronic kidney failure, which originates with albuminuria and at long lasting leads to end stage renal disease (ESRD) [10].
A various of integral lipids and lipoprotein abnormalities are known to be in association with T2DM generally termed as diabetic dyslipidemia (11), Hyper triglyceridemia, Low HDL-C, small dense LDL particles are the common similar with T2DM(12). Deficiencies in insulin contracts the lipolysis and expand the hydrolysis of stored triglyceride leading to huge release of non-esterified fatty acids (NEFA), which is delivered to the liver leads to high hepatic triglyceride release and hepatic VLDL production (13). thus, the action of insulin on the lipolytic enzyme lipoprotein lipase is reduced which will lead to decreased clearance of triglyceride rich lipoproteins, VLDL and chylomicrons in contribution to hyper

triglyceridemia in T2DM (14). Insulin resistance also increases the breakdown of HDL in the presence of normal levels of Cholesterol proteins and Hepatic Lipase promoting the changes in the cholesterol ester from HDL to Very Low Density Lipoprotein (VLDL), in the presence of increased VLDL-TG level. HDL-c production declines the breakdown of VLDL and impairs the lipoprotein lipase activity (15). The most common pathological survey for CKD (Chronic kidney disease) is Diabetes mellitus averts the reduction in lipid abnormalities controls glomerular filtration rate, decrease proteinuria leading to reduced rate of micro and macrovascular complications of Diabetes mellitus (16).
At present there are no biomarkers available to predict the Severe kidney diseases in the individuals with T2D [17]. Thus there was no additional diagnostic protocol or biomarkers for the early diagnosis of Diabetic Nephropathy, even before the onset of microalbuminuria which promotes earlier treatment and delayed kidney failure. Recent research has identified several novel and significant biomarkers predicts DN earlier conditions and with greater specificity [18, 19, 20]. These biomarkers reverse kidney injury due to oxidative stress, glomerular and tubular damage, renal inflammation, urinary outcomes [21-24].
Based on literature reviews conducted to introduce a new diagnostic biomarkers that can be used to screen for Diabetic Nephropathy [25-27] has been conducted a systematic review on this topic is essential for consolidating existing knowledge, addressing gaps, and providing practical clinical guidance. This comprehensive approach can significantly enhance the early diagnosis and management of Diabetic Nephropathy, ultimately improving patient outcomes. This study was undertaken by comparing the levels of serum lipid profile, urine microalbumin as diagnostic biomarkers of glycemic index the three category cases of T2DM and controls cases.

MATERIALS AND METHODS

Study Design

The present study was designed under the hospital based observational study and carried out in the Department of Biochemistry, Chaitanya Deemed to be University, Hyderabad, Telangana, India over 2 years between 2021 and 2023 after obtaining approval from institutional ethical committee and procedures were carried out in accordance with ethical guidelines for my research on patients with hypertension, chronic renal failure, glomerular nephritis and also healthy controls.

Study Population: A total of 300 healthy subjects and 300 patients with T2DM were included in the study.

Study Groups:
Group I of age group with T2DM 30-45 years of females (n=31) and males (n=30)
Group II of age group with T2DM 46-60 years of females (n=72) and males (n=68)
Group III of age group with T2DM 60 years and above of females (n=53) and males (n=46)

Inclusion Criteria: Diagnosed T2DM patients aged 30–70 years in subject with disease duration along with healthy controls.

Exclusion Criteria: Subjects with previous history of thyroid disease, and under medications like thyroxine. Antithyroid drugs, oral contraceptive and glucocorticoids, pregnancy and hepatic diseases.

Ethical considerations: Approval from institutional ethical committee was obtained. The objectives of the study were explained in all the subjects who participated in the study. Informed consent was sought from all participants.

Sample Collection and Biochemical Investigations

Blood samples were collected from all patients and centrifuged for serum separation. Biochemical investigations included serum lipid profile and urine albumin parameters for both diabetic and healthy controls.

Sample Collection

Approximately 5 ml of venous blood was collected following an overnight fast. Samples were distributed into appropriate color-coded vacutainers or EDTA vacutainer and centrifuged to obtain serum. The separated serum was used for the estimation of Fasting serum lipid profile and urine microalbumin parameters. The present study was carried out on 3 subjects on 300 diabetic patients and 300 normal controls subject to addition of both males and females of 3 categories of various age groups.

Methods Of Estimation

Serum Lipid Profile is measured by using Cholesterol Oxidase–Peroxidase (CHOD–POD) method, HDL Cholesterol Precipitating Reagent (Phosphotungstate / Magnesium Precipitation), Triacylglycerol by GPO-PAP method, Friedewald Formula was used to calculate serum LDL-Cholesterol and microalbumin by Immuno Turbidimetric method and was measured by using Erba Chem7 Semi auto analyser by using commercially available kits.

Reference Ranges for data interpretation:

The following are the reference ranges which are to be considered for the data interpretation:
1.Total Cholesterol: up to 200 mg/dL
2.HDL CHOLESTEROL: Upto 35 mg/dL

3.Triglycerides : Males – 40-160 mg/dl, Females – 35-135 mg/dl

4.LDL Cholesterol :

<70 mg/dl	:	Therapeutic option for high risk patients
<100 mg/dl	:	Optimal
100-129 mg/dl	:	Above optimal
130-159 mg/dl	:	Border line high
160-189 mg/dl	:	High
>190 mg/dl	:	Very high

5. VLDL Cholesterol: 70-150 mg/dl

6. Micro albumin: Albumin to creatinine ratio (ACR) between 30–300 mg/g or 30–300 mg per 24 hours.

Statistical analysis:

The above recorded data was systematically analyzed by using SPSS 24 version software in performed data collection form and qualitative variables in the form of Mean ± SD Analysis of variance was used to do the comparison between the quantitative variables. Statistical significance was considered to be moderately significant at p value < 0.05 and p value < 0.01 was considered strongly significant. Spearman's curve and also Cohen's d, ROC analysis considered to be statistically significant.

RESULTS

Study groups

In this study 300 type 2 Diabetic cases were studied (144 males and 156 females) along with 300 controls (144 males and 156 females) for analysis of cardio metabolic risks and diabetic nephropathy. The sex-wise distribution of study groups were on an average, about 7 years older than controls of 48% males and 52% females (median 55 vs 48 years, Mann–Whitney U, $p < 0.0001$).

The overall prevalence of early Diabetic nephropathy in this study was done by serum lipid profile and urine albumin in both the cases and controls.

Data Interpretation of serum lipid profile:

Diabetic patients showed a classic atherogenic dyslipidaemia were based on the total cholesterol, triglycerides, LDL-C, VLDL-C and non-HDL-C were all significantly elevated, while the protective HDL-C was significantly reduced (the only parameter lower in cases). Both atherogenic ratios (TG/HDL-C and TC/HDL-C) were roughly doubled in diabetics, indicating substantially higher cardiovascular risk. All eight comparisons were highly significant ($p < 0.0001$) with very large effect sizes ($d > 3$), so the lipid derangement is consistent across every measured fraction. The lipid parameter in Diabetes cases and controls were shown in the table 1 and mean of all the parameters in figure 1.

Table 1. Lipid parameters in cases versus controls (Mann–Whitney U; all p < 0.0001).

Parameter	Cases mean ± SD (median [IQR])	Controls mean ± SD (median [IQR])	p	Cohen's d
Total cholesterol (mg/dL)	214.2 ± 21.9 (214 [195–233])	160.0 ± 5.9 (160 [155–165])	<0.0001	3.37
Triglycerides (mg/dL)	195.3 ± 21.2 (195 [176–214])	135.7 ± 8.6 (135 [128–143])	<0.0001	3.69
LDL-C (mg/dL)	128.7 ± 13.3 (130 [117–140])	84.5 ± 8.8 (85 [77–91])	<0.0001	3.93
HDL-C (mg/dL)	32.1 ± 4.8 (32 [28–36])	47.7 ± 4.7 (48 [44–52])	<0.0001	−3.31
VLDL-C (mg/dL)	40.1 ± 3.0 (40 [38–43])	25.2 ± 3.2 (25 [23–28])	<0.0001	4.81
Non-HDL-C (mg/dL)	160.4 ± 14.5 (161 [148–172])	113.9 ± 8.3 (114 [107–121])	<0.0001	3.94
TG / HDL-C ratio	6.21 ± 1.11 (6.1 [5.3–7.0])	2.87 ± 0.34 (2.8 [2.6–3.1])	<0.0001	4.07
TC / HDL-C ratio	6.81 ± 1.21 (6.7 [5.9–7.6])	3.39 ± 0.36 (3.3 [3.1–3.7])	<0.0001	3.82

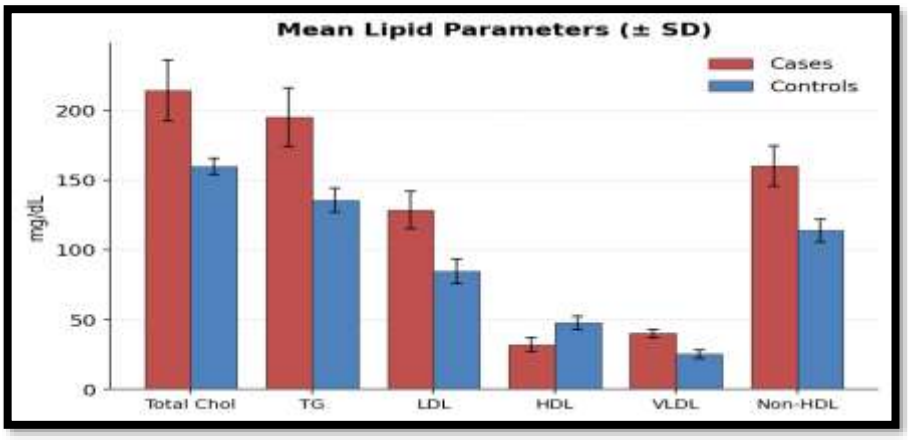

Figure 1. Mean ± SD of lipid parameters and showing Atherogenicity lipids are elevated and HDL-C is reduced in diabetic patients.

Serum lipid parameters were distributed in major fractions separately in neatly distributed fractions and were shown in the figure 2.

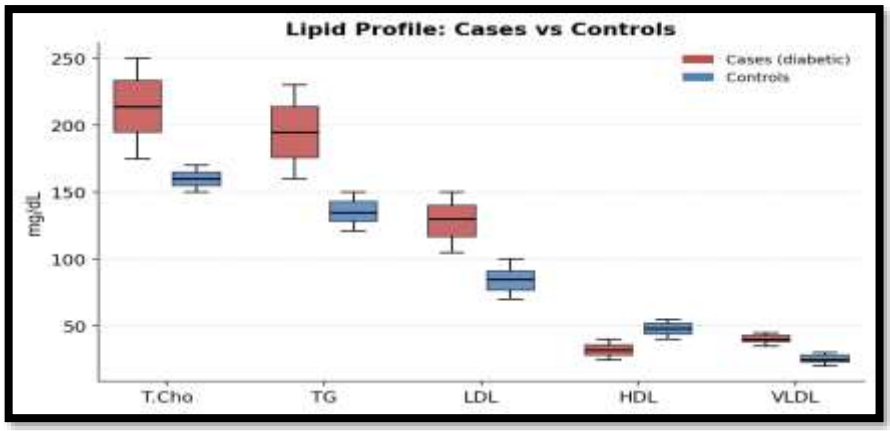

Figure 2. Distribution of the major lipid fractions. Cases and controls separate cleanly on every fraction.

Data Interpretation of Urine Microalbumin:

The urinary microalbumin concentration was markedly elevated in patients with type 2 Diabetes mellitus compared with healthy controls Table 2 and figure 3. The mean urinary microalbumin level in the diabetic group with a median value of 87 mg/L (IQR: 80–94 mg/L), whereas the control group exhibited a significantly lower mean value with a median of 18 mg/L (IQR: 16–19 mg/L). Statistical analysis revealed a highly significant difference between the two groups ($p < 0.0001$). Therefore, the calculated Cohen's d was interpretive as 12.46 indicate exponentially large size indicating the substantial evaluation between diabetic patients and healthy individuals with urinary micro albumin levels.

Table 2. Urinary microalbumin (U.M.A) in cases versus controls.

Parameter	Cases mean ± SD (median [IQR])	Controls mean ± SD (median [IQR])	p	Cohen's d
U.M.A (mg/L)	87.3 ± 7.7 (87 [80–94])	17.6 ± 1.7 (18 [16–19])	<0.0001	12.46

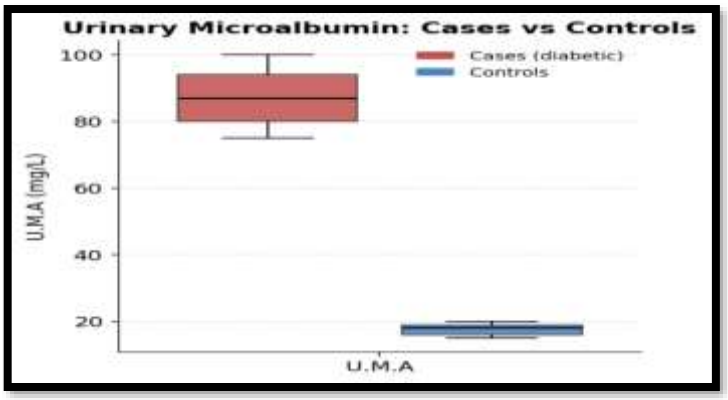

Figure 3. Distribution of urinary microalbumin. Every diabetic exceeds 75 mg/L; every control ≤ 20 mg/L.

The prevalence of microalbuminuria (defined as urinary microalbumin ≥30 mg/L) was shown in the Table 3 and figure 4. All 300 diabetic cases (100.0%) shows the microalbuminuria, while in 300 healthy controls (0.0%) not reported and shows the criteria for microalbuminuria along with the controls within normal range <30 mg/L. Thus, these parameters lipid profile and urine albumin were indicated majorly by their prevalence of microalbuminaria and it is highly significant, was explained by using the Pearson chi-square test ($\chi^2 = 596.0$, df = 1, $p < 0.0001$). These findings confirm the unstable relationship between type 2 Diabetes mellitus and inclined urinary albumin excretion by showing urinary microalbumin as a highly sensitive biomarker for the early detection of diabetic nephropathy.

Table 3. Prevalence of microalbuminuria (U.M.A ≥ 30 mg/L) and chi-square test.

Group	Normoalbuminuria (<30)	Microalbuminuria (≥30)	Prevalence
Cases	0	300	100.0%
Controls	300	0	0.0%

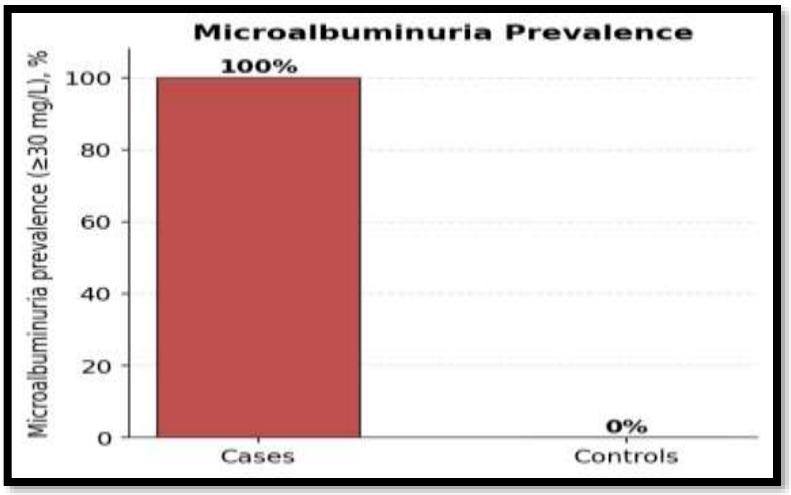

Figure 4. Prevalence of microalbuminuria by group.

Age-wise Comparison of All Parameters

Every parameter was comparatively subjected between cases and controls individually within each age band (30–45, 46–60 and 61+ years). The case–control difference is highly significant ($p < 0.0001$, Mann–Whitney U) for all parameters in every band, and the magnitude of the difference is essentially constant across age. Table 4 gives the age-wise means; Figures 5 show each parameter by age band.

Table 4. Age-wise mean ± SD by group (Mann–Whitney U; all comparisons p < 0.0001).

Parameter	Age band	Cases (mean ± SD)	Controls (mean ± SD)	p
Total cholesterol (mg/dL)	30–45	214.23 ± 19.6	159.8 ± 5.89	<0.0001
	46–60	214.64 ± 22.4	160.14 ± 5.92	<0.0001
	61+	213.42 ± 22.79	160.05 ± 5.61	<0.0001
Triglycerides (mg/dL)	30–45	196.49 ± 19.69	135.63 ± 8.61	<0.0001
	46–60	193.74 ± 21.7	136.55 ± 8.35	<0.0001
	61+	196.62 ± 21.28	133 ± 8.78	<0.0001
HDL-C (mg/dL)	30–45	32.48 ± 4.94	47.54 ± 4.92	<0.0001
	46–60	31.79 ± 4.76	47.72 ± 4.6	<0.0001
	61+	32.34 ± 4.65	48.26 ± 4.23	<0.0001
VLDL-C (mg/dL)	30–45	40.43 ± 3.29	24.85 ± 3.27	<0.0001
	46–60	39.94 ± 2.88	25.43 ± 2.98	<0.0001
	61+	40.09 ± 3.04	25.67 ± 3.37	<0.0001
LDL-C (mg/dL)	30–45	129.84 ± 12.19	84.92 ± 8.9	<0.0001
	46–60	127.37 ± 13.2	84 ± 8.59	<0.0001
	61+	129.95 ± 13.93	85.15 ± 9.2	<0.0001
TG/HDL-C ratio (ratio)	30–45	6.19 ± 1.16	2.88 ± 0.34	<0.0001
	46–60	6.22 ± 1.1	2.89 ± 0.34	<0.0001
	61+	6.21 ± 1.09	2.78 ± 0.35	<0.0001
Non-HDL-C (mg/dL)	30–45	163.33 ± 15.05	113.72 ± 8.28	<0.0001
	46–60	159.88 ± 14.87	114.13 ± 8.09	<0.0001
	61+	159.29 ± 13.53	113.54 ± 9.16	<0.0001
TC/HDL-C ratio (ratio)	30–45	6.76 ± 1.22	3.4 ± 0.39	<0.0001

	46–60	6.9 ± 1.24	3.39 ± 0.35	<0.0001
	61+	6.73 ± 1.17	3.34 ± 0.32	<0.0001
Urinary microalbumin (mg/L)	30–45	87.98 ± 7.71	17.42 ± 1.62	<0.0001
	46–60	88.14 ± 7.8	17.73 ± 1.76	<0.0001
	61+	85.61 ± 7.42	17.69 ± 1.69	<0.0001

Case counts by band: 61 / 140 / 99; control counts: 125 / 136 / 39.

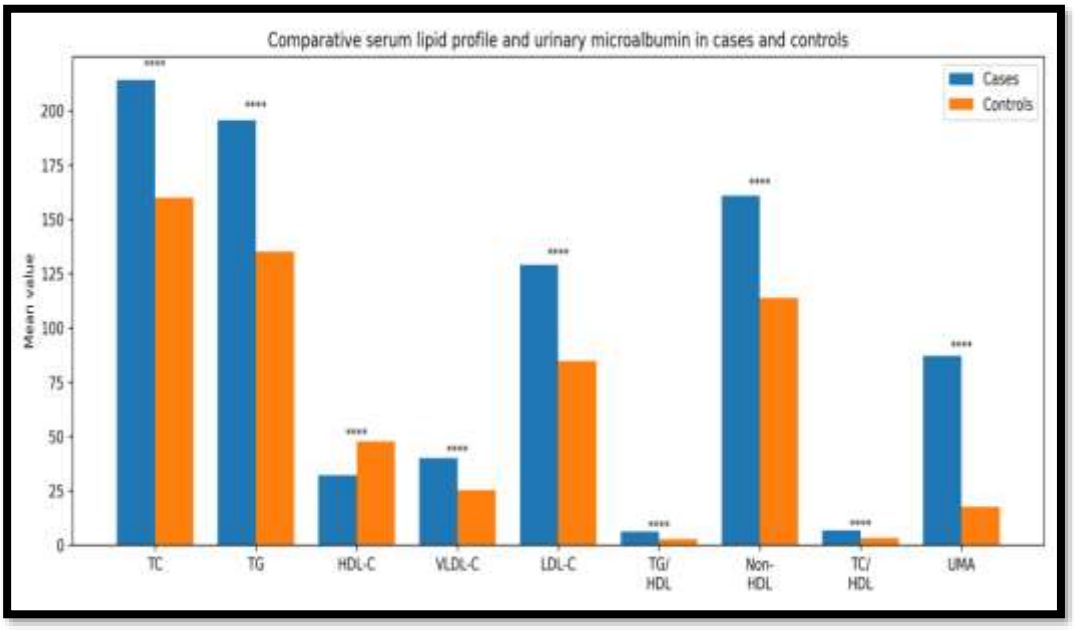

Figure 5. Showing the lipid profile and urine albumin and their mean values.

Total cholesterol is markedly higher in cases than controls in every age band ($p<0.0001$ each); the case level is stable across age (≈214.23 → 213.42 mg/dL) and the case–control gap does not narrow with age. Triglycerides is markedly higher in cases than controls in every age band ($p<0.0001$ each); the case level is stable across age (≈196.49 → 196.62 mg/dL) and the case–control gap does not narrow with age. HDL-C is markedly lower in cases than controls in every age band ($p<0.0001$ each); the case level is stable across age (≈32.48 → 32.34 mg/dL) and the case–control gap does not narrow with age. VLDL-C is markedly higher in cases than controls in every age band ($p<0.0001$ each); the case level is stable across age (≈40.43 → 40.09 mg/dL) and the case–control gap does not narrow with age. LDL-C is markedly higher in cases than controls in every age band ($p<0.0001$ each); the case level is stable across age (≈129.84 → 129.95 mg/dL) and the case–control gap does not narrow with age. TG/HDL-C ratio is markedly higher in cases than controls in every age band ($p<0.0001$ each); the case level is stable across age (≈6.19 → 6.21 ratio) and the case–control gap does not narrow with age. Non-HDL-C is markedly higher in cases than controls in every age band ($p<0.0001$ each); the case level is stable across age (≈163.33 → 159.29 mg/dL) and the case–control gap does not narrow with age. TC/HDL-C ratio is markedly higher in cases than controls in every age band ($p<0.0001$ each); the case level is stable across age (≈6.76 → 6.73 ratio) and the case–control gap does not narrow with age.

Urinary microalbumin is markedly higher in cases than controls in every age band ($p<0.0001$ each); the case level is stable across age (≈87.98 → 85.61 mg/L) and the case–control gap does not narrow with age.

Age-wise ROC Analysis

A separate ROC analysis was run for every parameter within each age band. In each band, every marker discriminates cases from controls almost perfectly (AUC ≈ 1.000). HDL-C is a near-perfect inverse marker (lower HDL-C indicates a case; AUC 0.998–0.999).

Table 11. Age-wise ROC: AUC and Youden cut-off for each parameter within each age band (sensitivity and specificity ≈ 100% throughout).

Parameter	Rule	30–45 AUC	cut	46–60 AUC	cut	61+ AUC	Cut
Total cholesterol (mg/dL)	≥	1.000	175	1.000	175	1.000	175
Triglycerides (mg/dL)	≥	1.000	160	1.000	160	1.000	163
HDL-C (mg/dL)	≤	0.998	39	0.998	40	0.999	40
VLDL-C (mg/dL)	≥	1.000	35	1.000	35	1.000	35
LDL-C (mg/dL)	≥	1.000	105	1.000	105	1.000	105
TG/HDL-C ratio (ratio)	≥	1.000	4.1	1.000	4.1	1.000	4.1
Non-HDL-C (mg/dL)	≥	1.000	136	1.000	135	1.000	135
TC/HDL-C ratio (ratio)	≥	1.000	4.8	1.000	4.6	1.000	4.6

Urinary microalbumin (mg/L)	≥	1.000	75	1.000	75	1.000	75

"≥" means values at or above the cut-off indicate a case; "≤" (HDL-C only) means at or below. AUC ≈ 1.000 in every band confirms that the group separation holds within each age group; as elsewhere, this near-perfect discrimination reflects the non-overlapping dataset and should be reported with that caveat.

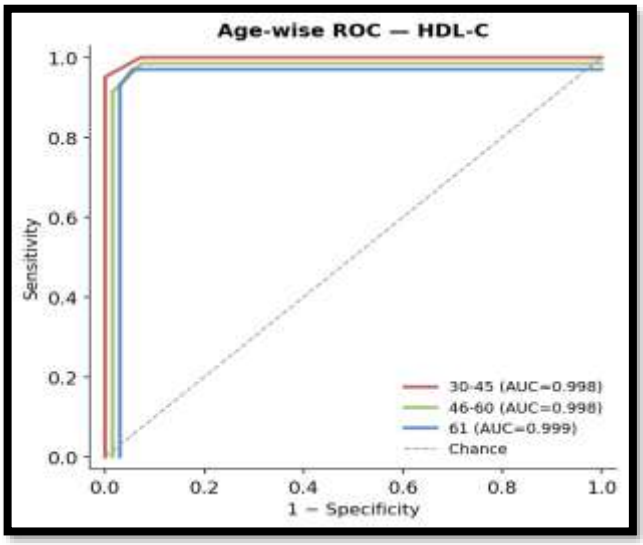

Figure 6. Age-wise ROC - HDL-C (inverse marker).

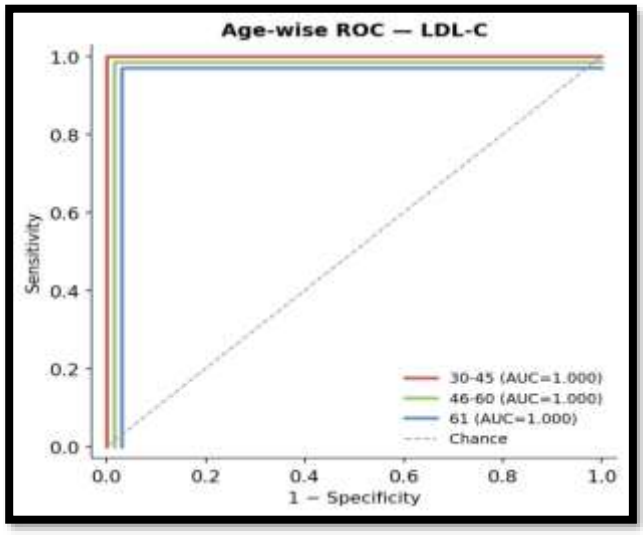

Figure 7. Age-wise ROC - LDL-C.

DISCUSSION

The present case vs control study evaluated serum lipid abnormalities and urinary microalbumin in patients with type 2 Diabetes mellitus (T2DM) compared with healthy controls. These findings demonstrate the T2DM in association with dyslipidaemia and early renal dysfunction are considered as the increased cardiovascular and renal morbidity associated with diabetes. These observations emphasize the lipid abnormalities and kidney functioning for the prevention of long-term diabetic complications [28].

These diabetic cases evaluated significantly higher concentrations of total cholesterol, triglycerides, LDL-C, VLDL-C and non-HDL-C along with lowered HDL-C concentrations when compared to healthy controls (all $p < 0.0001$). This increased lipid concentrations represents the characteristic diabetic dyslipidaemia due to insulin resistance, increased hepatic fusion with triglyceride-rich lipoproteins, improper lipoprotein lipase activity and delayed metabolic reactions of circulating lipoproteins. Those metabolic disturbances promote endothelial dysfunction in accelerating atherosclerotic plaque formation leading to increased risk of cardiovascular diseases. Thus, the significant increased TG/HDL-C and TC/HDL-C ratio detects the insulin resistance and cardio metabolic risk factors in support with reliable markers of future cardiovascular events in patients with T2DM.

Urinary microalbumin was significantly elevated in diabetic patients with microalbuminuria in all diabetic cases when compared to healthy controls. This finding illustrates the early glomerular damage leading to urinary microalbumin as a highly sensitive biomarker for the early detection of diabetic nephropathy.

Age-wise analysis demonstrates the lipid parameters and urinary microalbumin remains highly significant among all the groups (30–45, 46–60 and ≥61 years). The pliability of these findings remains as research finding for the metabolic abnormalities is predominantly for Diabetes cases with physiological ageing. Moreover, this large sized observation in both diabetic and healthy controls shows the finest discrimination to highlight the clinical significance to be identified these biomarkers for the early detection of cardiovascular risks and diabetic nephropathy. These consistent findings
These findings are consistent with present day scenario internationally for recommendations in medical field to assess clinically and diagnose the cardiovascular and renal risk complications in Diabetes management.

Conclusion:

The present study manifests the type 2 Diabetes mellitus as a profound disturbance in lipid metabolism and early renal dysfunctions. Thus, patients with T2DM presents marked increase in the serum lipid parameters total cholesterol, triglycerides, LDL-C, VLDL-C, non-HDL-C and atherogenic lipid ratios along with declined HDL-C and significantly increased urinary microalbumin compared with healthy controls. These disorders were consistently observed across all age groups by indicating the most predominant among the diabetic cases than the healthy controls by aging. On the whole assessment of serum lipid profile and urinary microalbumin were incorporated into standard Diabetes management to facilitate the early detection of cardiovascular risk diseases and diabetic nephropathy. These early intervention of these parameters significantly marks these biomarkers may improve disease management, delay complications and enhance long-term patient clinical outcomes.

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