RESEARCH PAPER

COMPARISON OF SERUM MEGALIN LEVELS WITH LIPID PROFILE AND ANTHROPOMETRIC MEASURES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Dr Namitha D[1*], Dr Asharani N[2], Dr Aliya Nusrath[3], Dr Rajeshwari A[4], Dr Shilpashree YD[5]

[1]Associate Professor, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya-571448. E mail drnamithad@bgs.edu.in*

[2] Former Professor and HOD, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya-571448.

[2]Professor and HOD, Department of Biochemistry, Alvas Institute of Medical Sciences and Research Centre, Moodubidire-574227.

[3]Vice Principal & Professor and HOD, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya-571448.

[4]Professor, Department of Biochemistry, Adichunchanagiri Institute of Medical Sciences, Adichunchanagiri University, BG Nagara, Nagamangala Taluk, Mandya- 571448.

[5]Professor, Department of Biochemistry, Farookh Academy of Medical Education, Mysore-571103.

ABSTRACT

Background: Diabetes Mellitus (DM) is a global non-communicable disease (NCD) linked to chronic low-grade inflammation and dyslipidemia, increasing the risk of atherosclerotic cardiovascular disease (CVD). Traditional lipid profiles may not fully capture this risk. Novel atherogenic indices and anthropometric markers may offer better predictive utility in diabetic populations. Megalin (LRP2), a multiligand endocytic receptor implicated in lipid handling and vascular pathology, has emerged as a potential novel biomarker in diabetes and atherosclerosis.

Objectives: To assess and compare anthropometric, glycemic, lipid and serum megalin levels in patients with type 2 diabetes mellitus (T2DM) and evaluate their association with the presence of cardiovascular disease (CVD).

Methods: This was a cross-sectional study conducted over 12 months with a total of 150 participants—100 T2DM patients (50 with CVD, 50 without) and 50 age- and sex-matched healthy controls. Data collected included anthropometric indices (BMI, waist-to-hip ratio), glycemic markers (FBS, PPBS), lipid profiles (HDL, LDL, VLDL, TC, TG), apolipoproteins, and atherogenic ratios. Serum Megalin was measured in all participants and compared across controls, diabetics without CVD, and diabetics with CVD. Statistical significance was set at $p<0.05$.

Results: Diabetics were significantly older than controls (mean age: 54.79 vs. 44.50 years, $p<0.001$). FBS and PPBS levels were significantly higher in diabetics ($p<0.001$). Diabetics exhibited higher waist circumference, BMI, and weight-to-height ratio than controls ($p<0.001$), indicating greater central obesity. Lipid abnormalities in diabetics included higher TG, LDL, VLDL, TC: HDL, TG:HDL ratios, and apolipoprotein B levels, and lower HDL and Apo A-I levels ($p<0.05$). Among diabetics, those with CVD were older (mean age 61.28 years), had longer diabetes duration (112.56 vs. 34.20 months), and higher FBS and LDL ($p<0.05$). Atherogenic indices such as TC: HDL and non-HDL cholesterol were significantly elevated in diabetics with CVD. Serum Megalin levels was declined from healthy individuals to diabetics with cardiovascular complications, implying that Megalin may be downregulated in relation to metabolic and vascular stress.

Conclusions: T2DM patients exhibit significant metabolic derangements and anthropometric alterations predisposing to CVD. Lipid ratios and apolipoproteins are superior to conventional lipid markers in identifying cardiovascular risk, and lower serum Megalin levels are associated with prevalent CVD in T2DM, although its standalone diagnostic performance is limited. Prolonged diabetes duration and abdominal obesity were strongly associated with CVD. Early and comprehensive risk assessment is crucial to improve cardiovascular outcomes in diabetic populations.

Keywords: Type 2 Diabetes Mellitus, Cardiovascular Disease, Dyslipidemia, Atherogenic Index, Apolipoproteins, Waist-Hip Ratio, Megalin, Anthropometry.

How to cite this article: Namitha D, Asharani N, Nusrath A, Rajeshwari A, Shilpashree YD. Comparison of serum megalin levels with lipid profile and anthropometric measures in patients with type 2 diabetes mellitus. Int J Drug Deliv Technol. 2026;16(8s): 253-263; DOI: 10.25258/ijddt.16.8s.26

INTRODUCTION

Diabetes Mellitus (DM) is a chronic, incurable, costly, but largely preventable non-communicable disease (NCD) which is responsible for millions of deaths annually, debilitating complications, and incalculable human misery [1]. World Health Organization (WHO) recognizes Diabetes

as one of the four major non-communicable diseases that require urgent attention from all key stakeholders, as it stands as the 3rd highest risk factor for premature mortality due to hyperglycemia [2,3].

Obesity, physical inactivity, smoking, dietary habits, psychological stress, and infections are seen as activating factors of the innate immune system, which induce chronic low-grade inflammation. This, in turn, stimulates secretion of pro-inflammatory cytokines, enhancing insulin resistance, and insulin resistance leads to type 2 diabetes mellitus (T2DM) [4].

Dyslipidaemia is another major metabolic abnormality that occurs in DM, with insulin resistance being the principal driving factor. Decreased High Density Lipoprotein (HDL) and increased triglyceride and Low-Density Lipoprotein (LDL) levels are considered atherogenic and constitute important risk factors for atherosclerotic cardiovascular disease (CVD) such as coronary artery disease [5]. However, conventional lipid parameters alone may not adequately capture the qualitative changes in lipoproteins that occur in diabetes. Modifications of lipoproteins by glycation and oxidation and/or variations in particle size distribution within major lipoprotein classes are not reflected in standard lipid profiles [6].

In recent years, apolipoproteins have emerged as important complementary biomarkers for CVD risk assessment. Apolipoprotein B (ApoB), representing the total number of atherogenic particles, and Apolipoprotein A-I (ApoA-I), the major protein component of HDL, offer a more direct quantification of atherogenic burden and protective potential, respectively. The ApoB/ApoA-I ratio has been shown to predict cardiovascular risk more accurately than traditional lipid measures, as it reflects both the balance between atherogenic and anti-atherogenic particles and the functional status of lipoproteins.

Similarly, atherogenic lipid ratios, derived from combinations of conventional lipid parameters such as total cholesterol/HDL-C, LDL-C/HDL-C, and triglycerides/HDL-C, provide a composite index of lipid-related risk. These ratios have been found to be superior to isolated lipid values in predicting subclinical atherosclerosis, insulin resistance, and future cardiovascular events in T2DM patients [7]. The incorporation of apolipoprotein measurements and atherogenic ratios into clinical evaluation can therefore enhance early detection of high-risk individuals, allowing for more targeted interventions.

Although LRP2 has not been suspected to participate in the direct causation of diabetes and its complications, studies on the interaction of renin–angiotensin components with megalin in the kidney, and on the ApoJ–LRP2 axis in the maintenance of normal glucose homeostasis and insulin sensitivity, support the potential cross-talk among organs and tissues (liver, kidney, skeletal muscle, and aorta). These findings further suggest a role of LRP2 in atherosclerosis development. Megalin (LRP2), a multiligand endocytic receptor implicated in lipid handling and vascular pathology, has emerged as a potential novel biomarker in diabetes and atherosclerosis.

Early assessment and control of CV risk factors in patients with T2DM—especially through the combined evaluation of traditional lipid parameters, apolipoproteins, serum megalin and atherogenic ratios—has a positive effect on reducing the risk of CVD and death, ultimately improving long-term prognosis.

MATERIALS AND METHODS

It was a Cross-sectional study conducted for a period of 12 months. Sampling method: Convenient sampling Sample size was 150 subjects

Study participants were clinically diagnosed type 2 diabetes mellitus with or without any complication (n=100) who admitted in Medicine and Surgical department of Adichunchanagiri hospital and research center were included in the study. Informed consent was obtained from the study participants and the study was approved by ethical and research committee to use human subjects in the research study. Age and sex matched healthy subjects were taken as controls (n=50).

Inclusion criteria

- Adults in the age group of >20 years with type 2 diabetes mellitus.
- Clinically diagnosed type 2 diabetes mellitus without any complication and clinically diagnosed type 2 diabetes mellitus with cardiovascular disease confirmed based on echocardiographic findings were included as cases.

Exclusion criteria

- Individuals who are unable or unwilling to take part in the clinical evaluation. Individuals who are suffering from hypertension, chronic diseases like cancer, end stage renal disease, thyroid disorders and liver diseases.
- Patient with Type 1 diabetes and secondary diabetes
- Patient with autoimmune disorders
- Patients with psychiatric disorders, primary hypertensive, pregnant women and those with gestational diabetes (GDM) will be excluded.
- Patient on lipid lowering agents.

METHOD OF COLLECTION OF DATA

Anthropometric measurement

- Waist circumference was measured at the point halfway between the lower border of ribs and the iliac crest in a horizontal plane and hip circumference will be measured at the widest level

over the greater trochanters and Waist-to hip ratio will be calculated

- The body mass index (BMI) was calculated by dividing the weight (kg) by height squared (m).
- The systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured in seated patients after 5 min of rest using a standard sphygmomanometer.

Blood samples were collected in fasting state and were analyzed for fasting blood glucose and serum lipid profile. 5ml of blood was drawn under aseptic condition from all subjects. This blood is allowed to clot and serum is separated. 2ml of blood was drawn during post-prandial period. Serum is used for the measurement of

Serum lipid profile –Enzymatic methods

Serum apolipoprotein A-I & B - Immunoturbidimetric method.

Laboratory Assessment

Table 1: Formulas and Clinical Interpretation of Apolipoprotein-Based Lipid Ratios in Cardiovascular Risk Assessment

Ratio Name	Formula	Interpretation
ApoB/ApoA-I Ratio	ApoB ÷ ApoA-I	<0.55 (men) and <0.50 (women) desirable; higher values strongly associated with CVD
ApoB/HDL-C Ratio	ApoB ÷ HDL-C	High values = higher atherogenic particle burden
ApoA-I/LDL-C Ratio	ApoA-I ÷ LDL-C	Lower values indicate higher risk

Serum Megalin assay: Fasting serum was stored at –20 °C until analysis. Serum Megalin concentrations were measured using a commercially available ELISA kit

STATISTICAL ANALYSIS

Data was entered into **Microsoft excel** data sheet. **Categorical data** was represented in the form of frequencies and proportions. C**ontinuous data** was tested by Kolmogorov–Smirnov test and the Shapiro–Wilk test for normal distribution, and further represented as mean and standard deviation. **Chi-square test** was used as test of significance for qualitative data. **Fischer's exact test** as well as **Yates correction** were used as test of significance for qualitative data which does not fulfill the criteria for Chi-square test (for 2x2 tables only). **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables. **Mann Whitney U test** was used as test of significance to identify the median difference between two quantitative variables with skewed distribution. **ANOVA (Analysis of Variance)** was the test of significance to identify the mean difference between more than two groups for quantitative data. Megalin levels were compared between the three study groups using one-way ANOVA with Tukey's post-hoc test. Correlations of Megalin with age, anthropometric indices, lipid parameters, ApoA-1/ApoB ratio, and atherogenic index of plasma were assessed using Pearson's correlation. **MS Excel** was used to obtain various types of graphs such as bar diagram, pie chart etc. **p-value** of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. **Statistical software: MedCalc** was used to estimate sample size. **MS Excel** and **SPSS-Software Version-26** were used to analyze the data in the study.

RESULTS

Table 2: Comparison of characteristics of the study subjects between controls and diabetics

Subjects (N=150)		Groups				p-value#
		Controls (N=50)		Diabetics (N=100)		
		N	%	N	%	
Age group	18-30 years	8	16.0%	2	2.0%	<0.001*
	31-45 years	19	38.0%	28	28.0%	
	46-60 years	19	38.0%	37	37.0%	
	>60 years	4	8.0%	33	33.0%	
Gender	Male	28	56.0%	64	64.0%	0.343
	Female	22	44.0%	36	36.0%	

#Chi-square test

* Statistically significant

Table 3: Comparison of mean age between controls and diabetics

Subjects (N=150)	Groups				p-value#
	Controls (N=50)		Diabetics (N=100)		
	Mean	SD	Mean	SD	
Age (in years)	44.50	11.41	54.79	13.26	<0.001*

Independent t-test
* Statistically significant

Tables 2 and 3 & Figure 1 showcases the distribution of age groups and gender between controls (n=50) and diabetic subjects (n=100). A significant proportion of diabetics are older, with a higher frequency in the >60 years group compared to controls (33% vs. 8%, respectively, p<0.001). Additionally, the mean age of diabetics significantly exceeds that of controls (54.79 ± 13.26 years vs. 44.50 ± 11.41 years, p<0.001), indicating an association between older age and diabetes prevalence. On other hand, in both groups, the male population is slightly more prominent than females (64% vs. 56% among diabetics and controls, respectively, p=0.343). These patterns suggest that the diabetic cohort is older males, likely contributing to their increased susceptibility to cardiovascular risks.

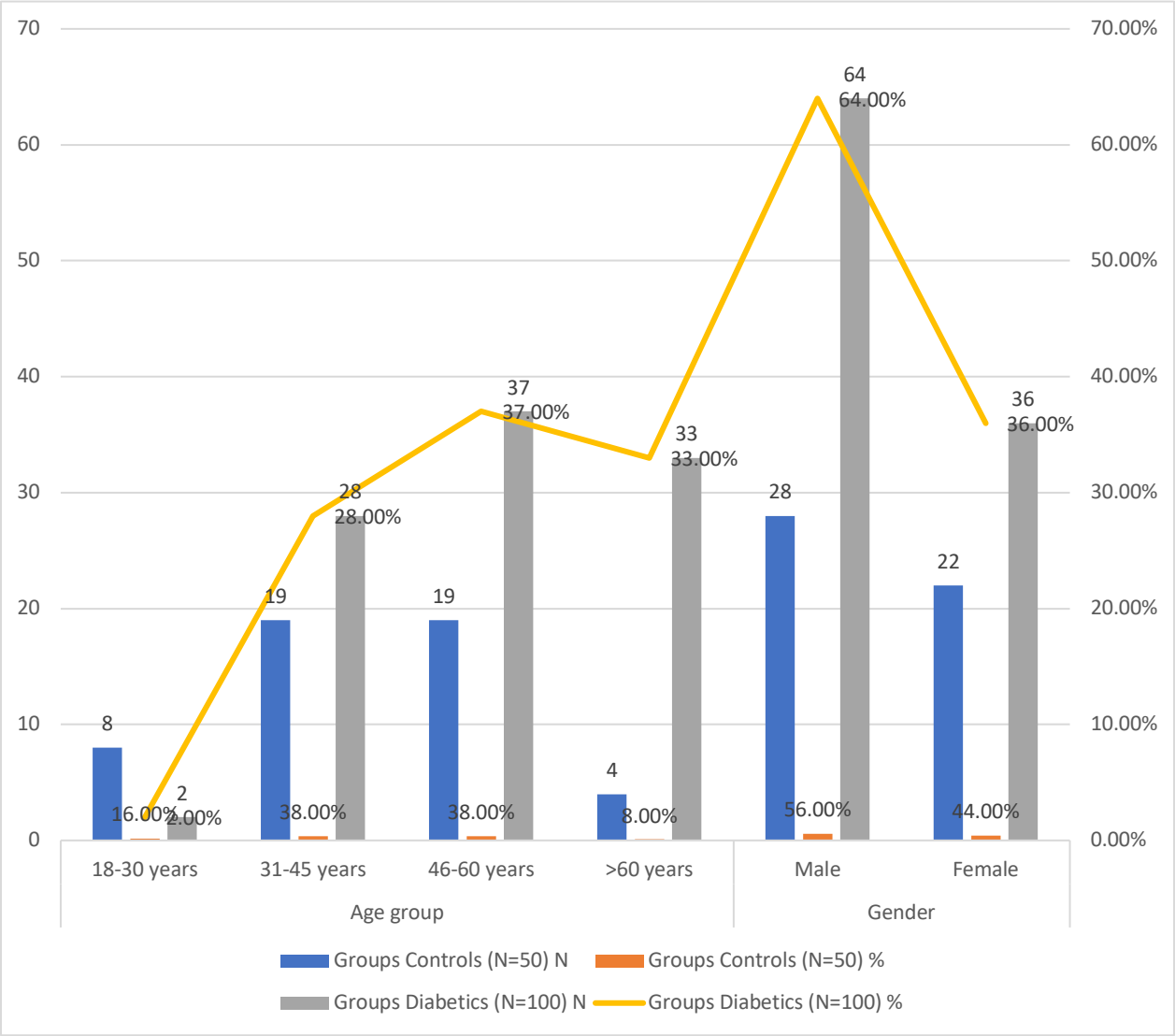


Figure 1-Distribution of age

Table 4: Comparison of characteristics of the study subjects between diabetics without CVD and with CVD

Subjects (N=100)		Groups				p-value#
		DM without CVD (N=50)		DM with CVD (N=50)		
		N	%	N	%	
Age group	18-30 years	2	4.0%	0	0.0%	<0.001*
	31-45 years	21	42.0%	7	14.0%	
	46-60 years	21	42.0%	16	32.0%	
	>60 years	6	12.0%	27	54.0%	

Gender	**Male**	32	64.0%	32	64.0%	1.000
	Female	18	36.0%	18	36.0%	
Duration of DM	**<5 years**	46	92.0%	0	0.0%	<0.001*
	6-10 years	4	8.0%	39	78.0%	
	>10 years	0	0.0%	11	22.0%	

Chi-square test
* Statistically significant

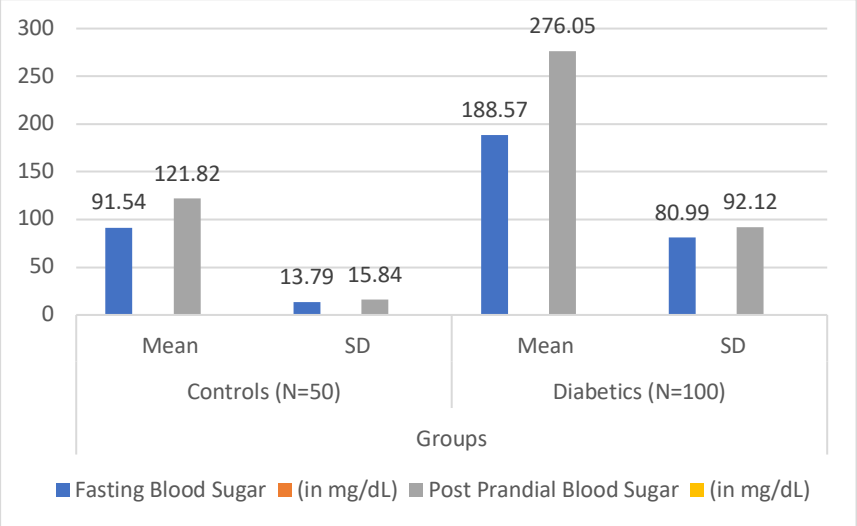
Table 5: Comparison of mean age between diabetics without CVD and with CVD

Subjects (N=150)	**Groups**				**p-value#**
	DM without CVD (N=50)		**DM with CVD (N=50)**		
	Mean	**SD**	**Mean**	**SD**	
Age (in years)	48.30	10.57	61.28	12.55	<0.001*

Independent t-test
* Statistically significant

Diabetics with CVD are predominantly older, with 54% above 60 years, compared to 12% in diabetics without CVD (p<0.001). Males are equally distributed across both groups (64%). A noteworthy detail is the prolonged diabetes duration among CVD patients, where 78% have 6-10 years of diabetes compared to only 8% in non-CVD diabetics. These characteristics reflect a significant age and diabetes duration link to cardiovascular events in diabetics, suggesting that chronic hyperglycaemia over time elevates cardiovascular risks.

Figure 2- Comparison of sugar profile between controls and diabetics



This figure delineates the sugar profile disparity between controls and diabetic patients, revealing significantly elevated fasting blood sugar (FBS) and post-prandial blood sugar (PPBS) levels in diabetics. The mean FBS in diabetics is 188.57 mg/dL, substantially surpassing the control mean of 91.54 mg/dL (p<0.001). Similarly, diabetic subjects display a pronounced PPBS (276.05 mg/dL) compared to controls (121.82 mg/dL, p<0.001). These findings illustrate the impaired glycemic control inherent in diabetics, which could predispose them to microvascular complications.

Table 6: Comparison of sugar profile between diabetics without CVD and with CVD

Subjects (N=100)	**Groups**				**p-value#**
	DM without CVD (N=50)		**DM with CVD (N=50)**		
	Mean	**SD**	**Mean**	**SD**	
Duration of DM (in months)	34.20	21.32	112.56	45.67	<0.001*
Fasting Blood Sugar (in mg/dL)	169.62	78.33	207.52	79.90	0.019*
Post Prandial Blood Sugar (in mg/dL)	260.34	93.85	291.76	88.51	0.088

Independent t-test
* Statistically significant

This table shows a marked increase in fasting blood sugar (FBS) in CVD-afflicted diabetics (207.52 mg/dL vs. 169.62 mg/dL in non-CVD diabetics, p=0.019), though post-prandial levels do not differ significantly (p=0.088). Duration of diabetes also demonstrates a notable disparity, with CVD diabetics averaging 112.56 months, significantly longer than the 34.20 months in non-CVD diabetics (p<0.001). These finding underscores prolonged hyperglycemia as a critical factor linked to cardiovascular disease in diabetics.

Table 7: Comparison of anthropometric parameters between controls and diabetics

Subjects (N=150)	Groups				p-value#
	Controls (N=50)		Diabetics (N=100)		
	Mean	SD	Mean	SD	
Waist Circumference (in cm)	91.05	8.12	101.62	12.48	<0.001*
Hip Circumference (in cm)	97.22	3.17	106.55	10.99	<0.001*
Waist:Hip Ratio	0.94	0.06	0.96	0.14	0.217
Weight (in kg)	68.32	4.36	72.96	4.16	<0.001*
Height (in cm)	164.48	5.50	164.92	5.75	0.655
Body Mass Index (in kg/m^2)	25.30	1.88	26.90	2.19	<0.001*
Weight:Height Ratio	0.55	0.05	0.62	0.08	<0.001*

Independent t-test
* Statistically significant

This table contrasts anthropometric measures, where diabetics exhibit higher waist circumference (101.62 cm) and hip circumference (106.55 cm) than controls (91.05 cm and 97.22 cm, respectively, p<0.001). The waist-to-hip ratio, though not statistically different, reflects central obesity in diabetics. Diabetics also have a higher mean BMI (26.90 kg/m² vs. 25.30 kg/m² in controls, p<0.001) and weight-to-height ratio (0.62 vs. 0.55, p<0.001). These observations imply an increased prevalence of obesity among diabetics, a major risk factor for cardiovascular complications.

Table 8: Comparison of anthropometric parameters between diabetics without CVD and with CVD

Subjects (N=100)	Groups				p-value#
	DM without CVD (N=50)		DM with CVD (N=50)		
	Mean	SD	Mean	SD	
Waist Circumference (in cm)	99.08	13.05	104.16	11.45	0.041*
Hip Circumference (in cm)	105.78	11.07	107.32	10.97	0.486
Waist:Hip Ratio	0.94	0.11	0.98	0.16	0.117
Weight (in kg)	72.12	3.64	73.80	4.50	0.043*
Height (in cm)	1.65	0.06	1.65	0.06	0.809
Body Mass Index (in kg/m^2)	2.73	0.19	2.72	0.19	0.106
Weight: Height Ratio	26.55	2.03	27.25	2.30	0.051

Independent t-test
* Statistically significant

Diabetics with CVD exhibit a significantly higher waist circumference (104.16 cm) than non-CVD counterparts (99.08 cm, p=0.041), while other parameters such as hip circumference and BMI remain similar. Weight shows a slight increase in the CVD group (73.80 kg vs. 72.12 kg, p=0.043). These results highlight abdominal obesity's importance as a risk factor in the cardiovascular health of diabetics, especially given the visceral adiposity link to metabolic syndromes.

Table 9: Comparison of lipid parameters between controls and diabetics

Subjects (N=150)	Groups				p-value#
	Controls (N=50)		Diabetics (N=100)		
	Mean	SD	Mean	SD	
Total Cholesterol (in mg/dL)	184.08	30.59	198.10	45.11	0.050*
Triglycerides (in mg/dL)	163.08	69.70	203.35	77.46	0.002*
High Density Lipoprotein (in mg/dL)	44.18	8.98	38.32	11.44	0.002*
Low Density Lipoprotein (in mg/dL)	107.48	31.36	122.14	40.91	0.027*

Very Low-Density Lipoprotein (in mg/dL)	32.20	13.91	40.86	16.09	0.001*
TC: HDL Ratio	4.38	1.37	5.63	2.17	<0.001*
TG: HDL Ratio	3.90	1.97	5.85	2.83	<0.001*
Non-HDL Cholesterol Ratio	139.90	33.73	159.78	42.47	0.005*
Atherogenic Index of Plasma	0.54	0.20	0.72	0.21	<0.001*
Apolipoprotein A-I (in mg/dL)	144.84	25.33	113.18	26.08	<0.001*
Apolipoprotein B (in mg/dL)	116.74	20.98	158.46	47.61	<0.001*
Apo A-I:Apo B Ratio	1.29	0.35	0.77	0.30	<0.001*

Independent t-test

* Statistically significant

In this table, diabetic individuals show elevated total cholesterol (198.10 mg/dL vs. 184.08 mg/dL, p=0.050) and triglyceride levels (203.35 mg/dL vs. 163.08 mg/dL, p=0.002) compared to controls. High-density lipoprotein (HDL) is notably lower in diabetics (38.32 mg/dL) than controls (44.18 mg/dL, p=0.002), while low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) levels are significantly higher in diabetics. Ratios like TC:HDL and TG:HDL also markedly increase in diabetics, underscoring dyslipidemia's role in enhancing cardiovascular risk in this group.

Table 10: Comparison of lipid parameters between diabetics without CVD and with CVD

Subjects (N=100)	**Groups**				**p-value#**
	DM without CVD (N=50)		**DM with CVD (N=50)**		
	Mean	**SD**	**Mean**	**SD**	
Total Cholesterol (in mg/dL)	189.68	47.13	206.52	41.78	0.062
Triglycerides (in mg/dL)	208.92	86.43	197.78	67.74	0.475
High Density Lipoprotein (in mg/dL)	38.84	10.51	37.80	12.39	0.652
Low Density Lipoprotein (in mg/dL)	111.98	33.42	132.30	45.32	0.012*
Very Low-Density Lipoprotein (in mg/dL)	41.30	17.30	40.42	14.96	0.787
TC: HDL Ratio	5.07	1.21	6.20	2.72	0.008*
TG: HDL Ratio	5.69	2.49	6.00	3.14	0.585
Non-HDL Cholesterol Ratio	150.84	41.28	168.72	42.15	0.035*
Atherogenic Index of Plasma	0.71	0.19	0.72	0.23	0.900
Apolipoprotein A-I (in mg/dL)	112.58	30.86	113.78	20.53	0.819
Apolipoprotein B (in mg/dL)	150.36	47.10	166.56	47.20	0.089
Apo A-I:Apo B Ratio	0.82	0.36	0.73	0.22	0.124

Independent t-test

* Statistically significant

In this table, LDL is significantly elevated in CVD-afflicted diabetics (132.30 mg/dL) compared to those without CVD (111.98 mg/dL, p=0.012). Ratios like TC:HDL and non-HDL cholesterol also show significant differences, with higher values in the CVD group (p=0.008 and p=0.035, respectively). These findings point toward a lipid profile pattern more conducive to atherogenesis in diabetics with CVD, indicating that dyslipidemia plays a crucial role in cardiovascular outcomes among diabetic patients.

Table 11: Descriptive Statistics of Serum Megalin (ng/mL)

Group	**Mean**	**95% CI (Lower–Upper)**	**Median**	**SD**	**Min**	**Max**	**IQR**	**Skewness**	**Kurtosis**
Controls	83.49	66.20 – 100.78	58.99	60.85	17.46	261.25	78.44	1.583	2.358
Diabetics w/o CVD	52.29	39.08 – 65.51	46.98	46.49	0.02	261.25	53.56	2.111	7.247
Diabetics with CVD	23.41	18.09 – 28.73	22.38	18.71	0.02	79.66	23.73	0.916	

Table 12: Comparison of Serum Megalin (ng/mL) Between Study Groups – ANOVA

Source of Variation	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**

Between Groups	90,281.632	2	45,140.816	21.795	<0.001
Within Groups	304,458.115	147	2,071.144		
Total	394,739.746	149			

There is a statistically significant difference in serum Megalin levels among the three groups ($p < 0.001$).

Table 13: Post Hoc Analysis (Tukey HSD) for Serum Megalin (ng/mL)

Comparison	Mean Difference (I–J)	Std. Error	p-value	95% CI (Lower–Upper)
Controls vs Diabetics w/o CVD	+31.19	9.10	0.002	9.64 – 52.74
Controls vs Diabetics with CVD	+60.08	9.10	<0.001	38.53 – 81.63
Diabetics w/o CVD vs Controls	–31.19	9.10	0.002	–52.74 – –9.64
Diabetics w/o CVD vs with CVD	+28.89	9.10	0.005	7.33 – 50.44
Diabetics with CVD vs Controls	–60.08	9.10	<0.001	–81.63 – –38.53
Diabetics with CVD vs w/o CVD	–28.89	9.10	0.005	–50.44 – –7.33

All differences marked with an asterisk () are statistically significant at the 0.05 level.*

Table 14: Homogeneous Subsets for Serum Megalin Levels (Tukey HSD Method)

Subset	Group	N	Mean Megalin (ng/mL)
1	**Diabetics with CVD**	50	23.41
2	**Diabetics without CVD**	50	52.29
3	**Controls**	50	83.49

Groups within each subset are not significantly different from each other, but across subsets, the differences are significant.

The analysis revealed significant differences in serum Megalin levels across the three study groups—healthy controls, diabetics without cardiovascular disease (CVD), and diabetics with CVD. Descriptive statistics showed that the mean Megalin concentration was highest in healthy controls (83.49 ng/mL, 95% CI: 66.20–100.78), followed by diabetics without CVD (52.29 ng/mL, 95% CI: 39.08–65.51), and lowest among diabetics with CVD (23.41 ng/mL, 95% CI: 18.09–28.73). A clear trend of declining Megalin levels was observed with increasing disease severity. The variability in values was notable, particularly in controls, with a wide range (17.46 to 261.25 ng/mL) and standard deviation of 60.85, while diabetics with CVD showed a narrower range (0.02 to 79.66 ng/mL) and lower standard deviation (18.71). Skewness and kurtosis values indicated moderate to high positive skew, particularly among diabetics without CVD (Skewness = 2.111; Kurtosis = 7.247), suggesting a right-tailed distribution in that group. The one-way ANOVA test confirmed that the differences in Megalin levels among the three groups were statistically significant ($F = 21.795$, $p < 0.001$). Post hoc analysis using the Tukey HSD method further revealed that each group was significantly different from the others. Specifically, the mean difference between controls and diabetics without CVD was +31.19 ng/mL ($p = 0.002$), and between controls and diabetics with CVD was +60.08 ng/mL ($p < 0.001$). Similarly, diabetics without CVD had significantly higher Megalin levels than those with CVD (mean difference = +28.89 ng/mL, $p = 0.005$). The homogeneous subset analysis classified the groups into three distinct subsets—controls, diabetics without CVD, and diabetics with CVD—each with non-overlapping means, underscoring the robustness of these differences.

Overall, these findings suggest a progressive decline in serum Megalin levels from healthy individuals to diabetics with cardiovascular complications, implying that Megalin may be downregulated in relation to metabolic and vascular stress. This positions Megalin as a potentially valuable biomarker for monitoring disease progression in type 2 diabetes mellitus.

Table 15. Correlation of Megalin with Age, Gender, BMI, and Waist/Hip Ratio

Variables	r	p-value	Significance
Age	–0.246	0.014	*Significant*
BMI	+0.071	0.482	Not significant
Waist/Hip ratio	–0.045	0.656	Not significant

Megalin showed a weak negative correlation with age that was statistically significant ($p = 0.014$), but no significant correlation with BMI or waist/hip ratio.

Table 16. Gender-wise Comparison (Independent Samples t-test)

Sex	N	Mean Megalin (ng/mL)	Std. Deviation	Std. Error Mean
Female	36	41.78	47.35	7.89

Male	64	35.64	32.01	4.00

Levene's Test for Equality of Variance: F = 1.402, $p = 0.239$, t-test for Equality of Means: $t = 0.770$, $p = 0.443$
There was no significant difference in serum Megalin levels between males and females ($p > 0.05$).

Table 17. Correlation of Megalin with Lipid Profile, ApoA-1/Apo B Ratio and Atherogenic Index of Plasma

Lipid Parameter	r	p-value	Significance
Total Cholesterol (TC)	–0.075	0.459	Not significant
Triglycerides (TG)	+0.046	0.650	Not significant
HDL	+0.147	0.143	Not significant
LDL	–0.176	0.081	Borderline
Non-HDL	–0.119	0.237	Not significant
ApoA-1/Apo B Ratio	+0.013	0.895	Not significant
Atherogenic Index (AIP)	**–0.056**	**0.583**	**Not significant**

A series of correlation and comparison analyses were conducted to explore the relationship of serum Megalin levels with various demographic, anthropometric, and biochemical parameters in patients with type 2 diabetes mellitus.

Table 15,16: Correlation of Megalin with Age, Gender, BMI, and Waist/Hip Ratio

Pearson correlation analysis revealed a weak but statistically significant negative correlation between age and Megalin levels ($r = –0.246$, $p = 0.014$), indicating that serum Megalin concentrations tend to decrease with advancing age in diabetic individuals. However, no statistically significant correlations were observed between Megalin and BMI ($r = 0.071$, $p = 0.482$) or waist-to-hip ratio ($r = –0.045$, $p = 0.656$), suggesting that central or general obesity might not directly influence circulating Megalin in this cohort. Additionally, an independent samples *t*-test comparing Megalin levels between sexes showed no significant difference between males (mean = 35.64 ± 32.01 ng/mL) and females (mean = 41.78 ± 47.35 ng/mL), with $p = 0.443$, implying that gender does not significantly affect serum Megalin concentrations in type 2 diabetic patients.

Table 17. Correlation of Megalin with Lipid Profile, ApoA-1/Apo B Ratio and Atherogenic Index of Plasma (AIP)

When correlated with lipid parameters, Megalin levels did not show any statistically significant association with total cholesterol ($r = –0.075$, $p = 0.459$), triglycerides ($r = 0.046$, $p = 0.650$), HDL cholesterol ($r = 0.147$, $p = 0.143$), or non-HDL cholesterol ($r = –0.119$, $p = 0.237$). However, a borderline negative correlation was observed with LDL cholesterol ($r = –0.176$, $p = 0.081$), indicating a possible inverse trend, though it did not reach statistical significance. These findings suggest that while Megalin may interact with lipid metabolism, its association with standard lipid markers is not strong enough to yield meaningful clinical implications in this diabetic sample. Serum Megalin levels also demonstrated no significant correlation with either the ApoA-1/Apo B ratio ($r = 0.013$, $p = 0.895$) or the Atherogenic Index of Plasma (AIP; $r = –0.056$, $p = 0.583$). These findings indicate that markers reflecting lipid particle balance or atherogenic risk, such as apolipoprotein ratios or logarithmic TG/HDL indices, do not significantly influence Megalin levels in patients with type 2 diabetes mellitus.

DISCUSSION

International Diabetes Federation (IDF) suggests that about 415 million people are diagnosed to have diabetes in the world with a prevalence rate of 8.8%. Out of this, 75% belongs to low- and middle-income countries. It is estimated that by 2040, about 642 million people will be diabetic with type 2 diabetes mellitus as the major type of diabetes [8].

Every 8 seconds, Diabetes kills and disables someone somewhere in the world. A large proportion of the four million people who die each year as a result of diabetes are in their most productive years (40-60 years), resulting in a high economic cost to society. Almost half of diabetes deaths occur in people under the age of 70 years; 55% of diabetes deaths are in women. Over the period, diabetes can damage the heart, blood vessels, eyes, kidneys, and nerves. Adults with diabetes have a two- to three-fold increased risk of heart attacks & strokes, it is one among the leading causes of kidney failure, diabetic retinopathy and increased risk of foot ulcers and neuropathy [9].

Y.-C. Chou et al. reported that apolipoprotein measurements significantly predict diabetes risk in an Asian population. Furthermore, the predictive ability of apo B alone to detect diabetes was comparable with that of the apo B/apo A-I ratio and better than the routine clinical lipid measurements [10].

In the present study, serum megalin levels showed a progressive decline from healthy controls to diabetics without CVD and were lowest in diabetics with CVD, and lower megalin independently predicted the presence of CVD among diabetic subjects. This pattern suggests that circulating megalin may be down-regulated or consumed with increasing metabolic and vascular burden and could

act as an adjunct marker of cardiovascular involvement in T2DM rather than a primary diagnostic biomarker. Recent human data from an Indian cohort similarly reported that serum megalin levels are altered in T2DM and that megalin alone has limited value as an isolated biomarker for cardiovascular disease, supporting the modest discriminative power observed in the present study [11].

Experimental work has shown that megalin is a multiligand endocytic receptor involved in reabsorption of lipoproteins and regulation of the renin–angiotensin system, thereby linking renal proximal tubule function with systemic atherosclerosis and vascular injury. Inhibition or knockdown of megalin reduces atherosclerotic burden in animal models, whereas alterations in renal Ang II content and cross-talk between kidney, liver and vasculature appear central to these effects. Furthermore, the ApoJ–LRP2 axis has been identified as a novel endocrine circuit in which megalin in skeletal muscle is required for normal insulin signalling and glucose uptake; disruption of this axis leads to insulin resistance and glucose intolerance, providing a mechanistic bridge between megalin, dysglycaemia and cardiovascular risk. Taken together with our findings, these data suggest that reduced circulating megalin in T2DM with CVD may reflect combined alterations in lipoprotein handling, renin–angiotensin activity and insulin signalling, and that serum megalin measurement may add incremental information when interpreted alongside apolipoproteins and atherogenic ratios in comprehensive cardiovascular risk assessment [12-14].

Wagner et al. have demonstrated that non-HDL cholesterol and Apo B show a similar raised pattern in hypertriglyceridemia diabetics, but Apo B identifies additional high-risk patients who have normal triglyceride levels. High Apo B levels were also found in almost half of the normocholesterolaemic type 2 diabetic patients [15].

Sniderman AD has shown that only 23% of diabetics have abnormal LDL, while 40% have abnormal Apo B. Diabetes per se increased Apo B concentration and Apo B is raised more frequently in coronary artery disease patients than LDL cholesterol [16].

Therefore, calculating or measuring LDL or VLDL cholesterol may not reflect the actual number of these atherogenic particles, while the plasma concentration of Apo B indicates their cumulative number [17].

CONCLUSION

T2DM patients exhibit significant metabolic derangements and anthropometric alterations that predispose to CVD. Lipid ratios and apolipoproteins are superior to conventional lipid markers in identifying cardiovascular risk. Prolonged diabetes duration and abdominal obesity are strongly associated with CVD. In addition, lower serum megalin levels are independently associated with the presence of CVD in T2DM, although its standalone discriminatory ability is limited, suggesting a potential role as an adjunct novel biomarker when interpreted alongside lipid ratios and apolipoproteins. Early and comprehensive, multiparametric risk assessment incorporating these markers is crucial to improve cardiovascular outcomes in diabetic populations.

REFERENCES

1. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Global Health 2013;1:339-49.
2. World Health Organization. Global Report on diabetes. Geneva, Switzerland: 2017.
3. Duncan BB. The burden of diabetes and hyperglycaemia in Brazil: past and present. Findings from the global burden of disease study 2015. Diabt Metab Syndr 2017;9:1-18.
4. Kavouras SA, Panagiotakos DB, Pitsavos C. Physical activity, obesity status, and glycemic control: the ATTICA study. Med Sci Sports Exerc 2007; 39: 606-11.
5. Palem SP, Abraham P. Atherogenic Index and Endothelial Dysfunction in Type 2 Diabetes Mellitus. Journal of Clinical and Diagnostic Research. 2018;12(6): 21-4.
6. Yo CC, Wen CW. Dyslipidemia and Diabetic Retinopathy. Rev Diabet Stud. 2013; 10:121-32.
7. Gowda YS, Rani NA, Rajeshwari A3, Somashekar G N4, Nusrath A. Atherogenic Predictor Indices: Role in Assessment of Cardiovascular Risk in Type 2 Diabetes Mellitus. Journal of Biotechnology and Biochemistry.2019;5(4):36-41.
8. International Diabetes Federation (IDF). Diabetes Atlas. 3rd edition. Brussels, Belgium: International Diabetes Federation. 2015.
9. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Global Health 2013;1:339-49.
10. Ching Y, Lin CS , Huey YC, Chan BY, Yu LC, Sun WYA. Utility of apolipoprotein measurements in predicting incident type 2 diabetes: A Chinese cohort study. Journal of the Formosan Medical Association. 2020;199(1):51-58.
11. Rajaragupathy S, Ponnusamy D, Balasundararaj D, Venkatesan S, Karthikeyan J. Serum megalin levels in type-2 diabetes mellitus with and without cardiovascular disease. Journal of Family Medicine and Primary Care. 2024 Nov 1;13(11):5240-3.

12. Seo JA, Kang MC, Yang WM, Hwang WM, Kim SS, Hong SH, Heo JI, Vijyakumar A, Pereira de Moura L, Uner A, Huang H. Apolipoprotein J is a hepatokine regulating muscle glucose metabolism and insulin sensitivity. Nature communications. 2020 Apr 24;11(1):2024.
13. Kukida M, Sawada H, Daugherty A, Lu HS. Megalin: a bridge connecting kidney, the renin-angiotensin system, and atherosclerosis. Pharmacological research. 2020 Jan 1;151:104537.
14. Cabezas F, Lagos J, Céspedes C, Vio CP, Bronfman M, Marzolo MP. Megalin/LRP2 expression is induced by peroxisome proliferator-activated receptor -alpha and -gamma: implications for PPARs' roles in renal function. PLoS One. 2011 Feb 2;6(2):e16794.
15. Wagner AM, Perez A, Calvo F, Bonet R, Castellvi A, Ordonez J. Apolipoprotein(B) Identifies Dyslipidemic Phenotypes Associated With Cardiovascular Risk in Normocholesterolaemic Type 2 Diabetic Patients. Diabetes Care. 1999;22:812-17.
16. Sniderman A, Lamarche B, Tilley J, Seccombe D, Frohlich J. Hypertriglyceridemic HyperapoB in Type 2 Diabetes. Diabetes Care. 2002;25(3):579-82.
17. Kanani FH, Alam JM. Apolipoprotein B in type 2 diabetes – a cross sectional study in a tertiary care set up. 2010;60(8):653-6.