Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 8 (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Assessment of Serum C-Reactive protein (CRP) to Albumin ratio and Serum Uric acid to Albumin ratio as markers of inflammation in patients with Type 2 Diabetes Mellitus

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Cite this paper as: Dr. Asha Kiran N, Dr. A.Sirish, Dr. K. Sravani, Dr. N. Ramakrishna, Dr. E. Kiran Kumar, (2025) Assessment of Serum C-Reactive protein (CRP) to Albumin ratio and Serum Uric acid to Albumin ratio as markers of inflammation in patients with Type 2 Diabetes Mellitus. *Journal of Neonatal Surgery*, 14 (8), 339-345.

ABSTRACT

Background: Diabetes Mellitus (DM) is a chronic condition that develops when the pancreas does not produce sufficient amount of insulin or the body cannot effectively utilize it. Uncontrolled type 2 diabetes mellitus (T2DM) is associated with the risk of developing micro- and macro-vascular complications. Inflammation is associated with the pathogenesis of T2DM.

Aim: This study aimed to assess the serum C-Reactive protein (CRP) to Albumin ratio (CAR) and serum Uric acid to Albumin ratio (UAR) as markers of inflammation in patients with Type 2 Diabetes Mellitus.

Materials and Methods: This retrospective study was conducted in the Department of Biochemistry in association with the Department of Pathology, Gayathri Vidhya Parishad Institute of Health Care & Medical Technology (GVPIHCMT), Visakhapatnam, Andhra Pradesh, India. After obtaining the Institutional Ethics Committee (GVPIHCMT/IEC/20250106/01), a total of 300 subjects' data was collected. Among 300 subjects, 150 were type 2 diabetes mellitus patients and 150 were non-diabetic subjects. Necessary details were collected from medical records, including demographic details, biochemical parameters such as fasting and post-prandial glucose, urea, creatinine, uric acid, lipid profile parameters, HbA1c, and CRP were retrospectively reviewed from the electronic file system and file records of the participants. CAR value is determined by dividing the CRP level with the albumin level, and UAR value is determined by dividing the uric acid level with the albumin level.

Results: In this study, a significant increase in mean age 51.5±10.3 years, BMI 27.5±2.2 kg/m^2, systolic blood pressure 120.5±6.8 mmHg, and diastolic blood pressure 78.5±4.4 mmHg was observed in T2DM patients compared with non-diabetic subjects. In biochemical parameters, significant increase in fasting blood sugar 160.8±59.8 mg/dl, post-prandial blood sugar 205.8±55.7 mg/dl, HbA1c 7.2±2.7 g%, urea 35.7±9.9 mg/dl, creatinine 1.1±0.1 mg/dl, uric acid 7.1±1.3 mg/dl, total cholesterol 185.2±44.1mg/dl, triglycerides 165.1±35.7 mg/dl, LDLC 122.4±32.5 mg/dl, VLDLC 33.0±7.1 mg/dl, total bilirubin 0.7±0.1mg/dl, AST 40.2±8.5 IU/L, ALT 41.9±9.6, ALP 99.6±22.5 IU/L and significant decrease in HDLC 29.8±4.5

mg/dl, total proteins 5.1±1.2 g% and albumin 3.0±0.9 g% was observed in T2DM subjects than non-diabetic subjects. In inflammatory markers, CRP 10.1±1.5 mg/dl, CAR 3.3±1.6, and UAR 2.3±1.4 were significantly increased in T2DM subjects than non-diabetic subjects. FBS was significantly correlated with CRP (r=0.439), CAR (r=0.351), and UAR (r=0.215). HbA1c also showed a positive correlation with CRP (r=0.269), CAR (r=0.296), and UAR (r=0.448).

Conclusion: This study results may conclude that significant increase in CRP, CAR, and UAR in patients with T2DM. Also, CRP, CAR, and UAR positively correlated with FBS and HbA1c.

Keywords: *Inflammation, Type 2 diabetes mellitus, C-Reactive protein (CRP) to Albumin ratio, Serum Uric acid to Albumin ratio*

1. INTRODUCTION

Diabetes Mellitus (DM) is a debilitating, chronic condition that develops when the pancreas does not produce enough insulin or the body cannot effectively utilize it. According to the International Diabetes Federation (IDF), the prevalence of diabetes, which was 10.5% in 2021, is projected to increase by 11.3% by 2030 and 12.2% by 2040. [1] In India, the burden of Type 2 Diabetes Mellitus (T2DM) is massive, with 77 million people, and ranks second in having the highest number of T2DM patients in the world, following China. [2]

Uncontrolled T2DM is associated with the risk of developing micro- and macro-vascular complications. In addition to the vascular complications, it was observed that T2DM patients had a 15% increased risk of premature death and an approximate 20-year reduced life expectancy. [3]

Inflammation is associated with the pathogenesis of T2DM. Many commonly coexisting conditions related to diabetes are thought to originate via inflammatory mechanisms. CRP and interleukin-6 (IL-6) are sensitive markers of subclinical systemic inflammation and are the most investigated inflammatory markers in diabetes. In addition, IL-1, IL-8, transforming growth factor-beta 1(TGF-β1), and tumor necrosis factor-alpha (TNF-α) were also investigated in T2DM. However, measurement of these inflammatory markers is not done routinely. [4]

C-reactive protein (CRP) and albumin are well-known acute-phase reactants (APR) and have been used as critical inflammatory biomarkers for predicting morbidity and mortality in many diseases. [5,6] CRP is synthesized by the liver and is produced in response to pro-inflammatory cytokines released from activated immune system cells, adipocytes, and is a sensitive marker of systemic inflammation. A meta-analysis of 18 prospective studies concluded that elevated levels of IL-6 and CRP are significantly associated with an increased risk of T2DM. [7]

Albumin, a negative acute-phase reactant, is produced by the liver. Serum albumin levels are decreased in individuals with chronic inflammation. Albumin provides the majority of the total antioxidant capacity of plasma, and it has been reported that decreased albumin levels may be associated with an increased risk of coronary heart disease, cardiovascular mortality, and carotid atherosclerosis. [8]

CRP to albumin ratio (CAR), a newly introduced indicator, is believed to be a more reliable predictor of the inflammatory status than CRP or albumin alone. The CAR has been used in the evaluation of prognosis and mortality in many diseases, including malignancies, as a prognostic score. [9]

Uric acid (UA), the final product of purine metabolism, is associated with oxidative stress, inflammatory responses, and endothelial dysfunction. Correlation between uric acid and the progression of diabetes has been widely reported. [10,11] However, the results were varied across the studies, and the exact role of uric acid in the prognosis of diabetes remains controversial. Some studies support that higher uric acid is associated with the progression of diabetes. [12,13] A recent study showed that higher serum uric acid levels were associated with increased risks of all-cause and cardiovascular mortality in diabetes. [14]

Albumin is the most abundant circulating protein in plasma, and it has various physiological functions. Serum albumin has been regarded as an indicator of nutritional status and it is also an important circulating antioxidant. [15] Therefore, the uric acid to albumin ratio (UAR) may coordinate nutritional status and oxidative stress to better predict the prognosis of diabetic patients.

Aim:

This study aimed to assess the serum C-Reactive protein (CRP) to Albumin ratio (CAR) and serum Uric acid to Albumin ratio (UAR) as markers of inflammation in patients with Type 2 Diabetes Mellitus.

2. MATERIALS AND METHODS

This retrospective study was conducted in the Department of Biochemistry in association with the Department of Pathology, Gayathri Vidhya Parishad Institute of Health Care & Medical Technology (GVPIHCMT), Visakhapatnam, Andhra Pradesh, India. After obtaining the Institutional Ethics Committee (GVPIHCMT/IEC/20250106/01), a total of 300 subjects' data was collected. Among them, 150 were type 2 diabetes mellitus patients and 150 were non-diabetic subjects.

Inclusion Criteria:

Age of study subjects ≥18 years, both males and females, T2DM, and non-diabetic subjects.

Exclusion criteria:

Patients with chronic inflammatory or autoimmune diseases, immunosuppressive therapy, morbid obesity, peripheral arterial disease, hematological diseases, diabetes type 1, hypertensive encephalopathy, malignancy, end-stage hepatic and renal disease, malnutrition, and pregnant women were excluded from the study.

Data collection:

Necessary details were collected from medical records, including demographic details like age, sex, BMI, and blood pressure were collected. Details of biochemical parameters such as fasting and post-prandial glucose by (GOD-POD method), urea (urease), creatinine (Jaffe's), uric acid (uricase), total cholesterol (cholesterol oxidase/peroxidase), Triglycerides (glycerol phosphate oxidase/peroxidase), HDL-C (HDLC- Direct). LDL-C (calculation), VLDL-C (calculation), HbA1c (HPLC), and CRP (quantitative immuno-turbidimetry) were retrospectively reviewed from the electronic file system and file records of the participants. The CAR value is determined by dividing the CRP level with the albumin level, and the UAR value is determined by dividing the uric acid level with the albumin level.

Statistical Analysis:

The data was represented in Mean±SD. Categorical variables were expressed in percentages. The Mann-Whitney *U* test was used for continuous non-normally distributed variables. Spearman's rho correlation was applied to correlate study parameters with FBS and HbA1c. the p-value of <0.05 is considered statistically significant. Data analysis was performed using SPSS software, version 22.0.

3. RESULTS

In this study, among 150 diabetic subjects, males were 90 (60%) and females were 60 (40%), whereas in non-diabetic subjects, males were 85 (56.6%) and females were 65 (43.4%). Significant increase in mean age 51.5±10.3 years, BMI 27.5±2.2 kg/m^2, systolic blood pressure 120.5±6.8 mmHg, diastolic blood pressure 78.5±4.4 mmHg was observed in T2DM patients compared with non-diabetic subjects.

Concerned with biochemical parameters, significant increase in fasting blood sugar 160.8±59.8 mg/dl, post-prandial blood sugar 205.8±55.7 mg/dl, HbA1c 7.2±2.7 g%, urea 35.7±9.9 mg/dl, creatinine 1.1±0.1 mg/dl, uric acid 7.1±1.3 mg/dl, total cholesterol 185.2±44.1mg/dl, triglycerides 165.1±35.7 mg/dl, LDLC 122.4±32.5 mg/dl, VLDLC 33.0±7.1 mg/dl, total bilirubin 0.7±0.1mg/dl, AST 40.2±8.5 IU/L, ALT 41.9±9.6, ALP 99.6±22.5 IU/L and significant decrease in HDLC 29.8±4.5 mg/dl, total proteins 5.1±1.2 g% and albumin 3.0±0.9 g% was observed in T2DM subjects compared with non-diabetic subjects.

Concerned with inflammatory markers, CRP 10.1±1.5 mg/dl, CAR 3.3±1.6 and UAR 2.3±1.4 were significantly increased in T2DM subjects than non-diabetic subjects as shown in table 1.

Table 1: Comparison of demographic details, biochemical, and inflammatory markers in T2DM patients and non-diabetic subjects

Parameters	T2DM cases (Mean±SD) (n=150)	Non-diabetic subjects (Mean±SD) (n=150)	p-value
Demographic Details			
Age (years)	51.5±10.3	47.6±9.9	0.000*
Males (n, %)	90 (60%)	85 (56.6%)	-
Females (n, %)	60 (40%)	65 (43.4%)	-
Body mass index (BMI) (kg/m^2)	27.5±2.2	22.1±1.5	0.000*

Systolic blood pressure (SBP) (mmHg)	120.5±6.8	114.5±4.4	0.000*
Diastolic blood pressure (DBP) (mmHg)	78.5±4.4	72.9±3.8	0.031*
Biochemical parameters			
Fasting blood sugar (FBS) (mg/dl)	160.8±59.8	88.4±9.9	0.000*
Post-prandial blood sugar (PPBS) (mg/dl)	205.8±55.7	128.7±12.7	0.000*
HbA1c (g%)	7.2±2.7	5.5±0.2	0.000*
Serum urea	35.7±9.9	25.7±8.8	0.000*
Serum creatinine	1.1±0.1	0.8±0.2	0.000*
Serum uric acid	7.1±1.3	4.1±1.2	0.000*
Serum total cholesterol	185.2±44.1	145.2±25.1	0.000*
Serum triglycerides	165.1±35.7	122.5±23.7	0.028*
Serum HDL-C	29.8±4.5	37.2±5.6	0.000*
Serum LDL-C	122.4±32.5	83.5±14.8	0.000*
Serum VLDL-C	33.0±7.1	24.5±4.7	0.020*
Serum total bilirubin (mg/dl)	0.7±0.1	0.4±0.1	0.023*
Serum direct bilirubin (mg/dl)	0.3±0.01	0.1±0.02	0.051
Serum AST (IU/L)	40.2±8.5	28.5±6.3	0.023*
Serum ALT (IU/L)	41.9±9.6	30.4±10.1	0.001*
Serum ALP (IU/L)	99.6±22.5	77.3±16.8	0.000*
Serum total proteins (g/dl)	5.1±1.2	6.2±1.4	0.007*
Serum Albumin (g/dl)	3.0±0.9	3.5±1.3	0.021*
Inflammatory markers			
Serum C-Reactive Protein (CRP) mg/dl	10.1±1.5	5.1±1.2	0.000*
CAR	3.3±1.6	1.4±0.9	0.004*
UAR	2.3±1.4	1.2±0.9	0.000*

* P<0.05, statistically significant

In this study, FBS was significantly correlated (positive) with CRP (r=0. 439), CAR (r=0.351), and UAR (r=0.215). HbA1c also showed a positive correlation with CRP (r=0.269), CAR (r=0.296), and UAR (r=0.448) as shown in Table 2.

Table-2: Spearman's rho correlation of inflammatory markers with FBS and HbA1c

Parameters	**FBS**		**HbA1c**	
	r-value	**p-value**	**r-value**	**p-value**
Serum C-Reactive Protein (CRP) mg/dl	0.439**	0.017	0.269*	0.012
CAR	0.351*	0.034	0.296*	0.019
UAR	0.215**	0.000	0.448**	0.000

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

4. DISCUSSION

Diabetes mellitus is a chronic systemic inflammatory disease of glucose metabolism. Uncontrolled hyperglycemia leads to many complications, most of which are associated with the duration of illness. These complications are associated with increased morbidity and mortality. [16]

In the present study, inflammatory markers such as CRP 10.1±1.5 mg/dl, CAR 3.3±1.6, and UAR 2.3±1.4 were significantly increased in T2DM subjects. Also, FBS was positively correlated with CRP (r=0.439), CAR (r=0.351), and UAR (r=0.215). Additionally, HbA1c also showed a positive correlation with CRP (r=0.269), CAR (r=0.296), and UAR (r=0.448).

Systemic inflammation is an underlying contributor to the pathophysiology of T2DM, and chronic subclinical inflammation is recognized as being common in the context of insulin resistance (IR). Several studies have demonstrated that the presence of inflammation predicts the development of T2DM. [17,18]

CRP, a well-known predictive marker for myocardial infarction (MI) and stroke in healthy subjects. Also been shown that elevated CRP levels are correlated with the severity of coronary artery disease (CAD), recurrent coronary events, and mortality in patients with stable CAD. [19] Additionally, CRP levels have been assessed to be a predictive marker for CAD in hypertension. Serum CRP levels are clinically used to predict the existence of cardiovascular events. [20]

In a study, by Wang et al., assessed the association between CRP levels and T2DM risk by conducting a meta-analysis and reported that elevated levels of CRP in healthy subjects are significantly associated with high-risk in T2DM. [21]

It has also been reported that CRP levels could be used to predict DM complications. in a recent study assessing the relationship between inflammatory markers and endothelial dysfunction in patients with DM. [17]

Recently, CAR has been proposed as a novel potential prognostic and systemic inflammation marker in cancer and a predictive marker for PCOS. In a recent study, Bayrak et al., reported serum CAR levels were significantly higher in complicated diabetic patients compared to controls. [22] Another study by Zeynep Caliskan et al., reported a positive correlation between CAR and BMI, fasting blood glucose, and HbA1c levels. [23] Yet another study by Gulali Aktas reported that high CAR levels were independently associated with an increased risk of diabetic nephropathy (DN). Elevated CAR levels may thus be considered a potential marker for DN in T2DM patients. [24] A study by Shuiying Li et al., reported a positive correlation between CAR and SC-MI among the US adult population, indicating the potential of CAR in enhancing SC-MI prevention strategies in the general population. [25] Therefore, calculating CAR is simpler and cheaper than measuring other inflammatory cytokines, such as IL-6 and TNF-α.

In this study, UAR levels were significantly increased in TDM patients and positively correlated with FBS and HbA1c. UAR was proposed as a novel biomarker that combines elements of nutrition, inflammation, and metabolic syndrome. Studies have indicated the close association between inflammation and the UAR. In support of our findings, a study by Chen S et al., reported that Age, UAR, and hsCRP were independent risk factors for all-cause death in diabetic patients after adjusting for potential confounding factors. [26] In a study by Jin S et al., reported that high levels of UAR are closely associated with the occurrence of T2DM-carotid atherosclerosis (CAS) and may serve as a useful biomarker for predicting T2DM-CAS. [27] Similarly, another study in a cohort of hypertensive patients showed that UAR is an independent predictor of high carotid intima-media thickness. [28] Another study proved that UAR can be used to predict major adverse cardiac and cerebral events in aortic stenosis patients after transcatheter aortic valve implantation. [29] Therefore, it is worth mentioning that UAR is a simple and cost-effective method because uric acid and albumin were routinely tested in diabetic patients.

5. CONCLUSION

This study may conclude that significant increase in CRP, CAR and UAR in patients with type 2 Diabetes Mellitus. Also CRP, CAP and UAR positively correlated with FBS and HbA1c. These markers may possibly serve as an inflammatory biomarker for patients with T2DM in clinical practice. CAR may be particularly relevant in evaluating the efficacy of new treatments targeting inflammation in T2DM. Further studies with large sample size are recommended.

Conflict of interest: Nil

Funding: Nil

Acknowledgements: We would like thank the authorities of Gayathri Vidhya Parishad Institute of Health Care & Medical Technology (GVPIHCMT), Visakhapatnam, Andhra Pradesh, India.

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