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ORIGINAL ARTICLE

C-Reactive Protein to Albumin Ratio in Patients with Prediabetes and Diabetes Mellitus: HbA1c and Inflammation

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SUMMARY

Background: **Inflammation has a significant status in both the pathogenesis and complications of diabetes mellitus (DM). The aim of this study is to compare the C-reactive protein (CRP) to albumin ratio (CAR) values in controlled DM, uncontrolled DM, prediabetes groups grouped by HbA1c as well as in a group of healthy individuals.**
Methods: **In this retrospective study, 6,993 DM patients, 770 prediabetes patients, and 1,340 healthy individuals were included. According to their HbA1c levels, DM patients were divided into two groups as controlled DM (HbAlc < 6.5%, n = 4,115) and uncontrolled DM (HbAlc ≥ 6.5%, n = 2,878).**
Results: **The CRP and CAR levels were significantly higher in the DM and prediabetes group than in the control group ($p < 0.05$, for both). Albumin levels were significantly lower in the DM group than in both the prediabetes and control groups ($p < 0.05$, for both). In the uncontrolled DM group, CRP and CAR values were found to be significantly higher than the control and controlled DM groups, while albumin values were significantly lower than the control group, prediabetes group, and controlled DM group ($p < 0.05$, for all).**
Conclusions: **It is thought that CAR, a liver related inflammatory marker, can be applied as an inflammation marker in both prediabetes, determined by HbA1c, and patients diagnosed with DM. Further prospective studies will better demonstrate the utility of CAR values as an inflammatory marker in DM and prediabetes.**
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KEY WORDS

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INTRODUCTION

Affecting millions of people in the world, diabetes mellitus (DM) is a metabolic disease that affects many systems at the micro and macrovascular level in the body [1]. Uncontrolled hyperglycemia and inflammation in DM increase morbidity and mortality with acute and chronic complications [1]. Used in the diagnosis and follow-up of DM, the HbA1c test is known to be a marker of vascular complications secondary to DM [1]. To prevent complications in DM, it is important to control the disease keeping the HbA1c below 6.5 [2].
Systemic markers of inflammation in DM are topical issues [3,4]. The markers of the systemic inflammatory

response include circulating white blood cells which originate from lymphoid/myeloid tissues and acute phase proteins such as C-reactive protein and albumin originating from the liver, and they expose the systemic response of these organs. Determined by serum C-reactive protein (CRP) and albumin levels, CRP/albumin ratio (CAR) is a commonly used liver-related parameter in the follow-up of systemic inflammation. CAR is shown to be significantly higher in cancer [5], infection [6], inflammatory diseases [7], and DM patients with complications [8].

To prevent DM complications, HbA1c levels are monitored. It is known that systemic inflammation is an important factor in the basis of complications. The relationship between CAR, which a liver-related marker of systemic inflammation that is associated with complications, and HbA1c, which is used in the follow-up of complications, has not been clearly indicated yet. In this study, our aim was to compare the CAR values in controlled DM, uncontrolled DM, and prediabetes groups grouped by HbA1c and in healthy individuals.

MATERIALS AND METHODS

This retrospective study was approved by Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (Approval Number 2021/187). Adult patients with DM and prediabetes and healthy individuals admitted to check-up polyclinics were included in the study. Age, gender, and the laboratory data including HbA1c, glucose, CRP, albumin, white blood cell count (WBC), neutrophil count, lymphocyte, platelet count, triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, urea, and creatinine were collected from the hospital information system. Then CAR was calculated as CRP value divided by albumin value (CRP/albumin ratio).

The patients with cancer, active infection, systemic inflammatory diseases, liver diseases, patients with CRP or albumin values not included in the reference values, as well as pregnant women were excluded from the study.

DM patients were divided into two groups according to their HbA1c values; above the 6.5 was regarded as the uncontrolled DM group and those below that level were regarded as the controlled DM group.

The statistical analyses were conducted using SPSS statistical software for Windows version 21 (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov test was used to see whether the parameters met the normality assumption. The explanatory statistics pertaining to the data not showing normal distribution were shown as medians (1st - 3rd quartile values) and the Kruskal-Wallis test was used to perform comparisons among the groups. When a significant difference was detected in the Kruskal-Wallis test, the post-hoc Dunn-Bonferoni test and adjusted p-values were used to determine the origin of the significance. Pearson's chi-squared test was used for the comparison of categorical variables. The diagnostic values of valuable parameters were assessed by receiver operating characteristic (ROC) and area under the ROC curve (AUC) with 95% confidence intervals (95% CI). Youden's Index in ROC curves was used to determine an optimum cutoff value of associated parameters and corresponding sensitivity (95% CI), specificity (95% CI) value for distinguishing. $p < 0.05$ was used as the significance level.

RESULTS

No difference was observed between DM, prediabetes, and control groups in terms of age and gender ($p = 0.887$ and $p = 0.112$, respectively). The CRP and CAR levels were significantly higher in the DM and prediabetes group than in the control group ($p < 0.05$ in both). Albumin levels were significantly lower in the DM group in comparison with both the prediabetes and control groups ($p < 0.05$ in both) (Table 1).

Having the DM group divided into two groups as controlled and uncontrolled based on HbA1c (< 6.5%) values, it was observed that male gender prevalence was higher in the uncontrolled DM group than in the other groups ($p < 0.05$, for all). CRP and CAR values were found to be significantly higher in the uncontrolled DM group compared to the control and controlled DM groups, while albumin values were found to be significantly lower than the control group, prediabetes group, and controlled DM group ($p < 0.05$, for all). In the controlled DM group, CRP values were found to be higher than the control group, but significantly lower than the prediabetes group ($p < 0.05$, for both). While CAR values were significantly higher in the controlled DM group in comparison with the control group ($p < 0.05$), albumin values were significantly lower ($p < 0.05$). Although there was no significant difference in albumin and CAR in the controlled DM group compared to the prediabetes group ($p > 0.05$, for both), CRP values were found to be significantly lower ($p < 0.05$). CRP and CAR values in the prediabetes group were significantly higher than the control group ($p < 0.05$, for both) (Table 2).

Receiver Operating Characteristic (ROC) analysis revealed that CAR had greater area under curve value among CAR (cutoff > 0.059, AUC: 0.569, sensitivity: 41.9%, specificity: 71.7%), CRP (cutoff > 3, AUC: 0.563, sensitivity: 30%, specificity: 82.8%), and albumin (cutoff ≤ 44, AUC: 0.560, sensitivity: 60%, specificity: 49.7%) in distinguishing DM and prediabetes patients from healthy volunteers ($p < 0.001$ for all) (Figure 1).

Table 1. Comparison of demographic and laboratory data between diabetes mellitus, prediabetes, and control groups.

	Control (n = 1,340)	Prediabetes (n = 770)	DM (n = 6,993)	p-value
Female gender, n (%)	910 (67.9%)	506 (65.7%)	4,542 (65.0%)	0.112
Age, years	59 (48 - 69)	58.5 (49 - 69)	60 (48 - 70)	0.887
C-reactive protein, mg/L	1.84 (1.4 - 2.7)	2.2 (1.5 - 3.2) *	2.2 (1.38 - 3.3) *	< 0.001
Albumin, g/L	44 (41.9 - 46.2)	43.8 (41.8 - 46)	43.3 (41 - 45.6) *, †	< 0.001
CAR	0.04 (0.03 - 0.06)	0.05 (0.03 - 0.07) *	0.05 (0.03 - 0.08) *	< 0.001
HbA1c, %	5.3 (5.1 - 5.5)	5.9 (5.8 - 6.1) *	6.1 (5.5 - 7.4) *, †	< 0.001
White blood count, 10^9/L	6.3 (5.3 - 7.6)	6.5 (5.4 - 7.66)	7.1 (5.96 - 8.56) *, †	< 0.001
Lymphocyte, 10^9/L	2.04 (1.7 - 2.5)	2.1 (1.7 - 2.6)	2.11 (1.67 - 2.,65) *	0.031
Neutrophil, 10^9/L	3.5 (2.8 - 4.35)	3.5 (2.7 - 4.4)	4.11 (3.29 - 5.19) *, †	< 0.001
Platelet, 10^9/L	251 (211 - 293)	251 (212 - 301)	254 (212 - 302)	0.110
Glucose, mg/dL	89 (82 - 96)	97 (89 - 107) *	107 (93 - 145) *, †	< 0.001
Triglyceride, mg/dL	103 (74 - 146)	132 (96 - 184) *	132 (93 - 191) *	< 0.001
Total cholesterol, mg/dL	182 (155 - 211)	190.5 (169 - 229) *	196 (167 - 224.3) *	< 0.001
LDL-cholesterol, mg/dL	116 (94.8 - 142)	133 (107 - 163) *	116.9 (92 - 142) †	< 0.001
HDL-cholesterol, mg/dL	55 (46.48 - 65)	55 (46 - 64)	49.9 (41.8 - 59.6) *, †	< 0.001
Urea, mg/dL	25 (21 - 31)	30 (24 - 38) *	30 (24 - 41) *	< 0.001
Creatinine, mg/dL	0.81 (0.73 - 0.93)	0.84 (0.75 - 0.97) *	0.82 (0.73 - 0.99) *	< 0.001

Values are given as median (1st - 3rd quartile) values and compared with Kruskal-Wallis test. Gender parameter was compared with Pearson Chi-Square test.
*** - Significantly different from the Control group according to Dunn-Bonferoni pairwise comparison test.**
† - Significantly different from the prediabetes group according to Dunn-Bonferoni pairwise comparison test.

Table 2. Comparison of demographic and laboratory data between uncontrolled diabetes mellitus, controlled diabetes mellitus, prediabetes, and control groups.

	Control (n = 1,340)	Prediabetes (n = 770)	Controlled DM (n = 4,115)	Uncontrolled DM (n = 2,878)	p-value
Female gender, n (%)	910 (67.9%)	506 (65.7%)	2,860 (69.5%)	1,682 (58.4%) *, †, ‡	< 0.001
Age, years	59 (48 - 69)	58.5 (49 - 69)	55 (41 - 67) *, †	65 (56 - 73) *, †, ‡	< 0.001
C-reactive protein, mg/L	1.84 (1.4 - 2.7)	2.2 (1.5 - 3.2) *	2.1 (1.3 - 3.2) *, †	2.35 (1.5 - 3.49) *, ‡	< 0.001
Albumin, g/L	44 (41.9 - 46.2)	43.8 (41.8 - 46)	43.7 (41.3 - 46) *	43 (40.3 - 45) *, †, ‡	< 0.001
CAR	0.04 (0.03 - 0.06)	0.05 (0.03 - 0.07) *	0.05 (0.03 - 0.07) *	0.05 (0.04 - 0.08) *, ‡	< 0.001
HbA1c, %	5.3 (5.1 - 5.5)	5.9 (5.8 - 6.1) *	5.6 (5.3 - 5.93) *, †	7.8 (7.0 - 9.4) *, †, ‡	< 0.001
White blood cell count, 10^9/L	6.3 (5.3 - 7.6)	6.5 (5.4 - 7.66)	6.88 (5.78 - 8.19) *, †	7.46 (6.27 - 9.0) *, †, ‡	< 0.001
Lymphocyte, 10^9/L	2.04 (1.7 - 2.5)	2.1 (1.7 - 2.6)	2.06 (1.64 - 2.56) †	2.2 (1.71 - 2.8.0) *, ‡	< 0.001
Neutrophil, 10^9/L	3.5 (2.8 - 4.35)	3.5 (2.7 - 4.4)	3.95 (3.18 - 4.97) *, †	4.35 (3.47 - 5.57) *, †, ‡	< 0.001
Platelet, 10^9/L	251 (211 - 293)	251 (212 - 301)	254 (213 - 302)	254 (210 - 301)	0.137
Glucose, mg/dL	89 (82 - 96)	97 (89 - 107) *	96 (89 - 107) *	154 (122 - 216) *, †, ‡	< 0.001
Triglyceride, mg/dL	103 (74 - 146)	132 (96 - 184) *	118 (84 - 167) *, †	157 (111 - 222) *, †, ‡	< 0.001
Total cholesterol, mg/dL	182 (155 - 211)	190.5 (169 - 229) *	196 (167 - 225) *	196 (168 - 224) *	< 0.001
LDL-cholesterol, mg/dL	116 (94.8 - 142)	133 (107 - 163) *	117.1 (92.2 - 142.4) †	116 (91.7 - 141) †	< 0.001
HDL-cholesterol, mg/dL	55 (46.48 - 65)	55 (46 - 64)	52 (43.7 - 62.3) *, †	46.9 (39.7 - 56) *, †, ‡	< 0.001
Urea, mg/dL	25 (21 - 31)	30 (24 - 38) *	29 (24 - 37) *	34 (26 - 44) *, †, ‡	< 0.001
Creatinine, mg/dL	0.81 (0.73 - 0.93)	0.84 (0.75 - 0.97) *	0.8 (0.72 - 0.94) †	0.86 (0.76 - 1.06) *, †, ‡	< 0.001

Values are given as median (1st - 3rd quartile) values and compared with Kruskal-Wallis test. Gender parameter compared with Pearson's chi-squared test. * - Significantly different from the Control group according to the Dunn-Bonferoni pairwise comparison test, † - Significantly different from the prediabetes group according to Dunn-Bonferoni pairwise comparison test, ‡ - Significantly different from the Controlled Diabetes mellitus group compared to the Dunn-Bonferoni pairwise comparison test.

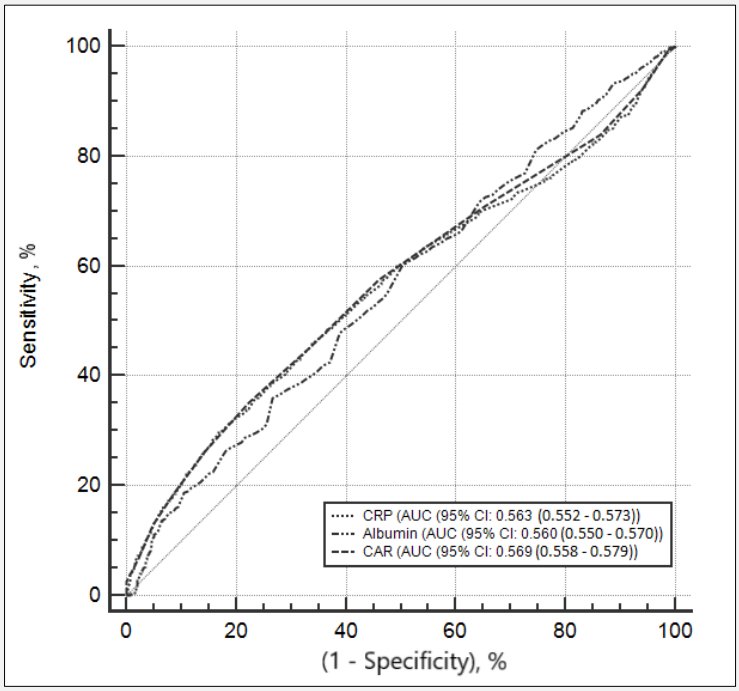

Figure 1. Receiver Operating Characteristic (ROC) analysis distinguishing DM and prediabetes patients and from healthy volunteers.

DISCUSSION

We aimed to show the importance of liver inflammation markers of systemic inflammation caused by DM, which is among the most common diseases causing Disability Adjusted Life Years (DALY) as a growing worldwide trend and are expected to affect 10% of the world's population in 2030 [9,10]. In this study, the relationship of HbA1c, which is known to be associated with DM complications [11], and CAR in terms of the role in systemic inflammation of the liver, the main organ where gluconeogenesis and the main cause of hyperglycemia in DM takes place [12,13], was indicated. CAR values were significantly higher in both prediabetes and DM groups in which glucose metabolism was impaired. When the DM group was divided into two groups as controlled and uncontrolled, significantly higher CAR values were found in the uncontrolled DM group compared to the prediabetes group, and the CAR values of all groups were significantly higher than the control group. This suggests that the disorder in glucose metabolism may be associated with systemic inflammation.

Besides being a predictive marker for predicting cardiovascular events [14], CRP values have been shown to be a risk factor for the development of type 2 DM in healthy individuals [15], as well as a marker that can be used to predict DM complications [16]. A meta-analysis demonstrated a decrease in insulin resistance with a decrease in CRP levels in patients with type 2 DM [17]. Moreover, a positive correlation has been shown among the insulin resistance and inflammatory markers such as CRP, IL-6, and TNF-Alpha [18]. Also, CRP levels are higher in type 2 DM patients [19]. Schalkwijk et al. revealed that CRP values are higher in patients with type 1 DM [20]. These findings show the presence of inflammation in DM disease. The fact that CRP levels were found to be high in prediabetes patients as well as in diabetic patients in our study supports the existence of inflammation in the deterioration of glucose metabolism that is not at the diabetes mellitus levels.

Albumin is a protein synthesized from the liver and regarded as an antioxidant and negative acute phase reactant [21,22]. Low levels of albumin are observed in conditions such as malnutrition-related diseases and inflammatory diseases [22,23]. Its levels have also been shown to decrease in those with insulin resistance [23,24]. In patients with type 2 diabetes, it has been shown that as a negative acute phase reactant, its synthesis from the liver is decreased [19]. Also, it is known that the albumin synthesis is decreased in insulin-dependent DM patients [25]. It has also been indicated that there is an inverse

correlation between HbA1c levels and albumin values in diabetic patients [26]. The data in our study show that, similar to the data seen in the literature, diabetic patients have lower albumin levels. It is thought that this situation may be related to the metabolic disorder in the liver caused by hyperinsulinemia due to insulin resistance in type 2 DM or the absence of insulin that stimulates protein synthesis in type 1 DM.

The relationship between CAR and inflammatory diseases and cancers has been a hot topic in recent research. One study showed that in Takayasu arteritis, the CAR values can be markers of both remission and disease activity [27]. It has been shown that the CAR values are higher in patients with rheumatoid arthritis than in healthy individuals [28]. A correlation between the disease severity and CAR has been shown in atherosclerosis-related coronary artery disease, in which inflammation plays an important role [29,30]. It is also shown to be a useful marker for predicting prognosis in patients with cervical cancer [31], ovarian cancer [32], renal cell carcinoma [33] , hepatocellular carcinoma [34], and cancer in general [35]. Likewise, in our study, the CAR values of prediabetic patients and DM patients, known to be associated with inflammation, were significantly higher than the healthy control group. In addition, ROC analysis also showed that the CAR values have the potential to be used to differentiate prediabetic and DM patients from the control group.

It is also indicated that the patients with type 2 DM, who have at least one of the complication of DM such as retinopathy, neuropathy, nephropathy and coronary artery diseases have higher CAR values than healthy volunteers [8]. In our study, the controlled DM group and prediabetes group had higher CAR values than the control group, whereas the CAR values in the uncontrolled DM group were found to be higher than both the control and prediabetes groups. The absence of proper control of DM, which is one of the most important factors in the development of DM complications, and higher CAR values in patients who develop complications are thought to indicate the relationship between complication and inflammation. The fact that no difference was observed in CAR values between the controlled DM with HbA1c levels below 6.5 and prediabetes groups as well as, the higher CAR values in the uncontrolled DM group with HbA1c values above 6.5, show that controlling DM with treatment also decreases the inflammation.

In order to ensure that CRP and albumin values, which are known to be associated with many conditions due to the retrospective design of our study, did not change for a reason other than DM or prediabetes. Only the files of the patients who applied for DM follow-up or DM investigation were included after checking their compliance with our inclusion and exclusion criteria. At the same time, to exclude the mentioned other conditions, only patients whose CRP and albumin values were within the reference ranges were included in the study. In our study, despite the fact that the CRP and albumin values were within the reference range, higher CAR values were found in the DM and prediabetes groups than in the control group, indicating that DM and prediabetes are associated with inflammation. Considering the findings of our study that have recently focused on inflammatory processes for the prevention and better treatment of diabetes [36], our study suggests that CAR values may be included instead of CRP and albumin when evaluating DM and prediabetes patients with normal CRP and albumin values. In addition, the findings obtained in DM and prediabetic patient groups suggest that it may be necessary to determine new reference ranges for CRP and albumin in DM and prediabetic patients by prospectively designed reference range studies in patients with DM or prediabetes, in which all other diseases are excluded.

Our study has some limitations. The main limitation of the study was its retrospective design. We studied the values for albumin, CRP and CAR, which are liver-related inflammatory markers, whereas the other inflammatory markers such as systemic neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, erythrocyte sedimentation rate, and interleukin-6 were not included in our study. Furthermore, there are many studies on inflammation with DM, the importance of our study is that emphasizes the fact that the inflammation process can also be an important indicator in the prediabetes period.

CONCLUSION

We think that CAR values, as liver-related inflammatory markers, can be used as an indicator of inflammation in prediabetes patients determined by HbA1c and in diagnosed DM patients, even if CRP and albumin values are within the reference range in both prediabetes and DM patients. With studies conducted on the relationship between the change in HbA1c levels and the change in CAR values, it is thought that its place in treatment follow-up will be revealed more clearly. Further prospective studies will be able to better demonstrate the usability of CAR values as an inflammatory marker in DM.

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None.

Declaration of Interest:
None.

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