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ORIGINAL ARTICLE

Increased serum levels of ischemia-modified albumin and C-reactive protein in type 1 diabetes patients with ketoacidosis

Shao-gang Ma · Yue Jin · Wei Xu · Wen Hu · Feng Bai · Xiao-juan Wu

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Abstract Ischemia-modified albumin (IMA) levels have been advocated as a biomarker for evaluating the oxidative stress status. No data are showed on the potential role of IMA in type 1 diabetes (T1D). We aimed to establish the correlation among serum levels of IMA, C-reactive protein (CRP), and diabetic ketoacidosis (DKA) in patients with T1D. Fifty-seven patients with T1D, 27 patients with DKA, and 40 controls were enrolled. Serum IMA and CRP levels were measured and evaluated to distinguish from DKA. CRP and IMA levels were significantly elevated in patients with DKA at admission to the hospital compared to non-DKA and control subjects. CRP and IMA levels were higher in non-DKA patients than in controls. CRP, plasma glucose, and IMA levels were reduced after insulin treatment. Serum IMA levels were an independent risk marker for DKA ($OR = 1.225$, $p = 0.002$, 95 % CI: 1.076–1.394). Receiver operating characteristic curve analyses showed no difference in the areas under curve for serum IMA and CRP values. This study indicates that IMA and CRP levels were significantly correlated with DKA diagnosis. IMA can act as a biomarker that reflects the presence of DKA.

Keywords Ischemia-modified albumin · C-reactive protein · Diabetic ketoacidosis · Type 1 diabetes · Biomarker

S. Ma (✉) · W. Xu · W. Hu · F. Bai · X. Wu
Department of Endocrinology and Metabolism, The Affiliated Huai'an Hospital of Xuzhou Medical College, No. 62 South Huaihai Road, Huai'an 223002, China
e-mail: mashaogang@163.com

Y. Jin
Department of Clinical Laboratory, The Affiliated Huai'an Hospital of Xuzhou Medical College, Huai'an 223002, China

Introduction

It is known that serum ischemia-modified albumin (IMA) levels are elevated in patients with cerebrovascular diseases [1, 2], end-stage renal disease [3], and liver cirrhosis [4]. IMA has been advocated as a non-specific biomarker for evaluating the oxidative stress status or atherosclerosis burden in patients with diabetes [3–5].

Diabetic ketoacidosis (DKA) is an acute, potentially life-threatening complication of type 1 diabetes (T1D). The cause of DKA was significantly different from that of atypical type 2 diabetes. Most of atypical type 2 diabetes such as ketosis-prone diabetes had history of excessive ingestion of sugar-containing soft drink [6]. Most DKA patients require intensive, in-hospital treatment [7]. It has been suggested that DKA can be associated with the non-infectious form of the systemic inflammatory response [8]. Free radicals and pro-inflammatory cytokines are released during DKA, and C-reactive protein (CRP) and inflammatory cytokine levels are increased in DKA patients [9]. CRP is a type I acute-phase response protein synthesized in the liver [10]. Previous studies have shown that the classical marker CRP has a potential value for evaluating DKA [8, 9].

Previous studies have reported that type 2 diabetes (T2D) patients with chronic complications have higher serum IMA and CRP levels compared with healthy controls [5, 11–13]. However, to the best of our knowledge, no data are shown on the potential role of IMA in T1D. Both chronic and acute diabetic complications are potent producers of free radicals and pro-inflammatory cytokines in patients with T1D [14, 15]. We hypothesize that free radicals may modify albumin in patients with DKA. In addition, the change of IMA can provide more predictive value to DKA. The routine measurement of CRP and IMA are

daily performed at our medical center. In the present study, we investigated and evaluated the IMA and CRP levels in T1D patients with and without ketoacidosis. We also assessed the association among serum IMA and metabolic parameters in these subjects.

Subjects and methods

Patient recruitment and exclusion criteria

This controlled study was performed at the endocrinology and emergency center of a medical college–affiliated hospital from January 2010 to October 2011. The study was approved by the ethical committee of the hospital. Informed consent was obtained from all of the participants.

Fifty-seven consecutive patients with T1D, 27 patients with DKA, and 40 normal control subjects (Table 1) participated in the study. The blood tests, such as complete blood count, blood chemistries, and cardiac enzymes were performed in all the participants. Electrocardiogram and chest digital radiography were also finished. Patients with DKA had an admission plasma glucose >13.90 mmol/L, a urine ketone level defined as moderate to large (+ to +++), and a arterial pH value <7.30. We also utilized the criteria for the measured arterial pH values to classify the severity of the DKA: mild, 7.20≤pH<7.30; moderate, 7.10≤pH<7.20; and severe, pH <7.10 [7, 16].

We excluded patients who were pregnant or had acute alcohol intoxication, acute pancreatitis, chronic renal failure, congestive heart failure, hepatic insufficiency, inflammatory conditions, ischemic events, and lactic acidosis. Controls without clinical evidence of a major disease underwent a routine medical check-up. All patients with DKA received medical treatment in the form of nutrition and insulin therapy. Patients were monitored until DKA was resolved and the patient was discharged from the hospital.

Anthropometry and biochemical assays

The body mass index was calculated as the body weight in kilograms divided by the height in meters squared. After a 10-h fast, blood samples were drawn from the subjects by venipuncture into vacutainer tubes. In the DKA group, the blood samples were drawn at admission before initial therapy and at 120 h after the administration of fluids and insulin.

The blood samples were centrifuged and stored at −20 °C for a maximum of 4 weeks before the IMA measurement. Serum IMA levels were measured using a commercial kit (Co-Health (Beijing) Laboratories Co., Ltd., Beijing, China) on an Olympus AU 2700 autoanalyzer (Olympus, Tokyo, Japan). Serum CRP levels were measured by the immunonephelometric method (Dade Behring Marburg, Marburg, Germany). The values determined as normal were <77.6 U/mL for IMA and <3.0 mg/L for CRP. The intra-assay variability for IMA and CRP was below 4.0 %. Glycated hemoglobin A1c (HbA1c) levels were measured using an HbA1c Meter from Bio-Rad Laboratories, Ltd. (Shanghai, China). The final HbA1c test result was converted from the percent HbA1c to HbA1c in mmol/mol. Laboratory tests included a metabolic profile, arterial blood gas analysis, and other routine chemistries,

Table 1 Clinical and biochemical characteristics of the study participants

Variable	Controls ($n = 40$)	Non-DKA ($n = 30$)	DKA ($n = 27$)
Female/male (n/n)	24/16	18/12	11/16
Age (years)	49.34 ± 12.09	49.32 ± 13.78	46.64 ± 17.86
Duration of diabetes (years)	N/A	4.63 ± 1.16	4.13 ± 1.04
Systolic blood pressure (mmHg)	120 ± 15	130 ± 18	110 ± 11*,§
Diastolic blood pressure (mmHg)	80 ± 10	87 ± 9	75 ± 6*,§
Body mass index (kg/m^2)	23.63 ± 1.10	25.10 ± 2.52	24.23 ± 2.01
Plasma glucose (mmol/L)	5.10 ± 0.81	10.33 ± 2.26**	17.22 ± 1.42**,§§
Glycated hemoglobin A1c mmol/mol	38 ± 2	89 ± 6**	115 ± 10**,§§
%	5.60 ± 0.24	10.34 ± 2.71**	12.71 ± 3.13**,§§
Osmolality (mosm/L)	293.47 ± 10.85	299.81 ± 21.09	308.23 ± 13.05*,§
Total cholesterol (mmol/L)	4.41 ± 0.93	4.63 ± 1.20	4.82 ± 2.63
Triglycerides (mmol/L)	1.62 (0.26–3.78)	2.03 (0.56–8.51)	2.12 (0.57–6.87)
High-density lipoprotein cholesterol (mmol/L)	1.31 ± 0.30	1.24 ± 0.48	1.23 ± 0.44
Low-density lipoprotein cholesterol (mmol/L)	2.80 ± 0.78	2.59 ± 1.01	2.85 ± 0.55

Comparison to control group: * $p < 0.05$, ** $p < 0.001$; comparison to non-DKA group: § $p < 0.05$, §§ $p < 0.001$. All values in the table are given as the mean ± standard deviation, except for the triglyceride values given as the median and the range (min–max)

which were performed by routine clinical assays in the hospital laboratory.

Statistical methods

Quantitative data are presented as the mean ± standard deviation. Statistical analyses were conducted using the SPSS 11.0 package for Windows (SPSS Inc., Chicago, IL). A comparative analysis among the three groups was carried out using the Student Newman-Keuls ANOVA. Chi-square tests were utilized for the comparison of other clinical features. Paired *t* tests were utilized to determine the significance of changes in the DKA cases between the admission and resolution laboratory values. The correlations between IMA and other variables were examined by Pearson's correlation test as well as a multiple linear regression analysis. The risk markers for the diagnosis of DKA were examined by multiple logistic analysis. To determine the optimal cutoff values and the diagnostic performance of the variables, a receiver operating characteristic (ROC) curve analysis was performed. The area under curve (AUC) was also used to determine the discriminative power in the diagnosis of DKA. A two-tailed p value <0.05 was considered statistically significant.

Results

Clinical characteristics

The baseline demographic and clinical characteristics of the subjects are shown in Table 1. A total of 97 cases were included in the study. HbA1c and plasma glucose levels were significantly higher in the DKA and non-DKA groups than in the control group ($p < 0.001$). The glycemic variables (plasma glucose, HbA1c) and osmolality (Osm) were higher in the DKA group than in the non-DKA and control groups ($p < 0.001$ and $p < 0.05$, respectively). With respect to age, gender, body mass index, and lipid profiles, there were no significant differences among the three groups. The difference of duration of diabetes between the DKA and non-DKA groups did not reach statistical significance. Both the systolic and diastolic blood pressures were lower in the DKA group than in the control and non-DKA groups ($p < 0.05$).

The clinical and laboratory characteristics of the patients before treatment initiation according to the severity of DKA at admission [7] are shown in Table 2. There were seven patients with severe DKA, 11 patients with moderate DKA, and nine patients with mild DKA. There were no significant differences in the CRP and IMA levels among the mild, moderate, and severe DKA cases (data not shown). The arterial pH and the levels of HCO_3, β-Hydroxybutyrate, plasma glucose, CRP, and IMA were significantly different in the moderate/severe DKA patients compared to the mild DKA patients (all $p < 0.05$). No differences were found among the mild and moderate/severe groups with respect to age, body mass index, gender, HbA1c levels, and Osm levels of the patients.

IMA and CRP levels

The mean CRP level was 1.39 ± 0.53 mg/L in the control group, 2.66 ± 1.01 mg/L in the non-DKA group, and 4.88 ± 1.81 mg/L in the DKA group. The difference among the three groups was statistically significant ($p < 0.05$). For pairwise group comparisons, statistically significant differences were observed between the DKA and non-DKA groups ($p < 0.001$), the DKA and control groups ($p < 0.001$), and the non-DKA and control groups ($p < 0.05$). These results are shown in Fig. 1.

Table 2 Demographic information and laboratory values for patients with DKA at their admission ($n = 27$)

Variable	Admission		*p*
	Mild DKA	Moderate/severe DKA	
Female/Male (n/n)	4/5	7/11	0.310
Age (years)	55 ± 14	43 ± 20	0.111
Body mass index (Kg/m^2)	22.67 ± 1.53	23.50 ± 0.74	0.440
Plasma glucose (mmol/L)	16.90 ± 2.14	22.81 ± 11.22	0.023
Glycated hemoglobin A1c mmol/mol	118 ± 13	102 ± 18	0.459
%	12.95 ± 3.36	11.45 ± 3.83	
Serum HCO_3 (mmol/L)	12.83 ± 3.64	6.90 ± 3.090	<0.001
Arterial pH	7.24 ± 0.03	7.05 ± 0.14	<0.001
β-Hydroxybutyrate (mmol/L)	6.24 ± 1.02	8.26 ± 1.31	0.014
Osmolality (mosm/L)	301.67 ± 12.48	310.07 ± 4.90	0.689
C-reactive protein (mg/L)	4.70 ± 2.35	6.70 ± 1.35	0.038
Ischemia-modified albumin (U/mL)	81.59 ± 16.00	107.41 ± 19.58	0.041

All values in the table are given as the mean ± standard deviation

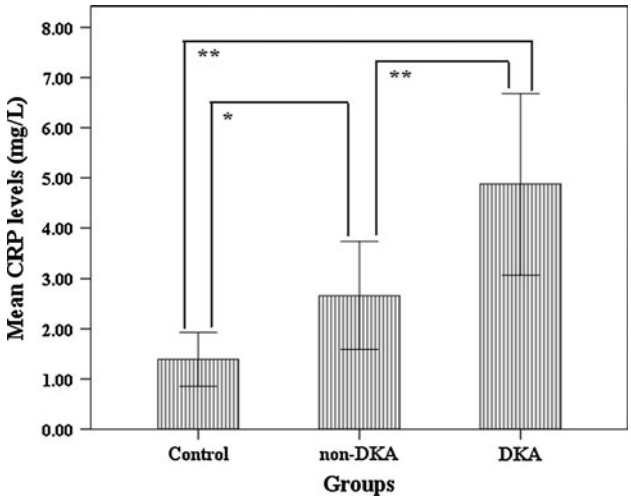

Fig. 1 Mean CRP levels in the control, non-DKA, and DKA groups with the statistical significance of comparisons between groups indicated as the following: $*p < 0.05$, $**p < 0.001$

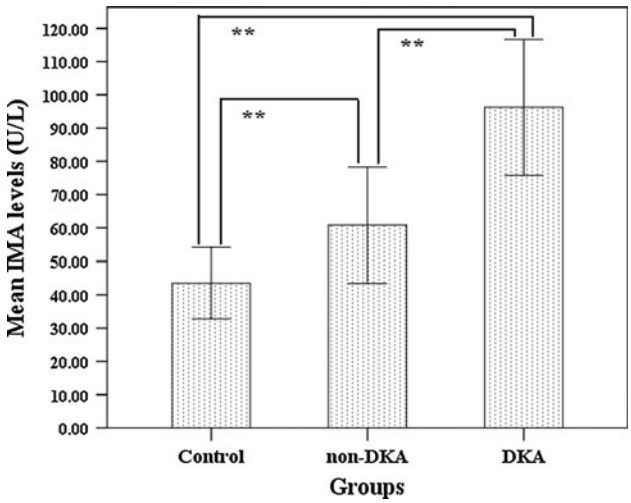

Fig. 2 Mean IMA levels in the control, non-DKA, and DKA groups with statistically significant comparisons between groups indicated as the following: $**p < 0.001$

The mean serum IMA level was 43.48 ± 10.67 U/mL in the control group, 60.82 ± 17.41 U/mL in the non-DKA group, and 96.22 ± 20.45 U/mL in the DKA group. The difference among the three groups was statistically significant ($p < 0.001$). As shown in Fig. 2, serum IMA levels were significantly higher in the T1D groups (both DKA and non-DKA) compared with the control group ($p < 0.001$), and the level was higher in the DKA group than in the non-DKA group ($p < 0.001$).

At the resolution of DKA after treatment, CRP, IMA, and plasma glucose levels were significantly reduced in the DKA patients (for final concentrations of 2.56 ± 1.18 mg/L, 66.27 ± 9.34 U/mL, 6.97 ± 2.10 mmol/L, respectively) compared to the concentrations of those biomarkers on admission ($p = 0.025$, $p < 0.001$, $p = 0.004$, respectively). The HCO_3 levels, Osm, and pH returned to normal values after DKA resolution (data not shown).

Correlation and regression analyses

Bivariate correlation analyses were performed to assess relationships among baseline serum IMA and CRP concentrations and metabolic parameters in subjects with diabetes. There was positive correlation between CRP and IMA levels ($r = 0.450$, $p = 0.001$) and IMA and plasma glucose levels ($r = 0.395$, $p = 0.006$) for the patients with T1D. Multiple regression analysis showed that DKA was independent of factor influencing baseline serum IMA and CRP levels ($\beta = 0.586$, $p < 0.001$; $\beta = 0.608$, $p < 0.001$, respectively). To examine the risk markers of DKA, multiple logistic regression analyses with the three significant clinical variables (CRP, IMA, and plasma glucose) were performed. The odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated. The differences in DKA prevalence for varying CRP and IMA levels were statistically significant ($OR = 0.825$, $p = 0.042$, 95 % CI: 0.876–1.014; and $OR = 1.225$, $p = 0.002$, 95 % CI: 1.076–1.394 for CRP and IMA, respectively). Elevated IMA levels may be a suitable risk marker for the diagnosis of DKA.

ROC analyses

ROC analysis was used to identify the optimal serum IMA and CRP cutoff values for DKA prediction (Fig. 3). We observed no statistically significant differences between the AUC for IMA (0.929 ± 0.053) and CRP (0.904 ± 0.061) ($z = 0.370$, $p = 0.711$). The optimum diagnostic cutoff for IMA that maximally increased sensitivity and specificity in the estimation of DKA was 79.67 U/L (for a sensitivity and specificity of 81.2 and 89.5 %, respectively). For CRP, this point was calculated as 4.0 mg/L (for a sensitivity and specificity of 64.7 and 95.5 %, respectively). The comparison of sensitivity and specificity between CRP and IMA did not reach statistical difference ($p = 0.080$, $p = 0.250$, respectively), when the optimum diagnostic cut-off in the estimation of DKA is evaluated.

Discussion

The possible role of IMA in various diseases has been confirmed in previous studies. It was suggested that IMA may act as a biomarker for ischemia-related diseases or an individual's oxidative stress status [1–5, 11–13]. Higher level of IMA in type 2 diabetic patients confirms that it may be of non-cardiac origin [17]. In this study, IMA and

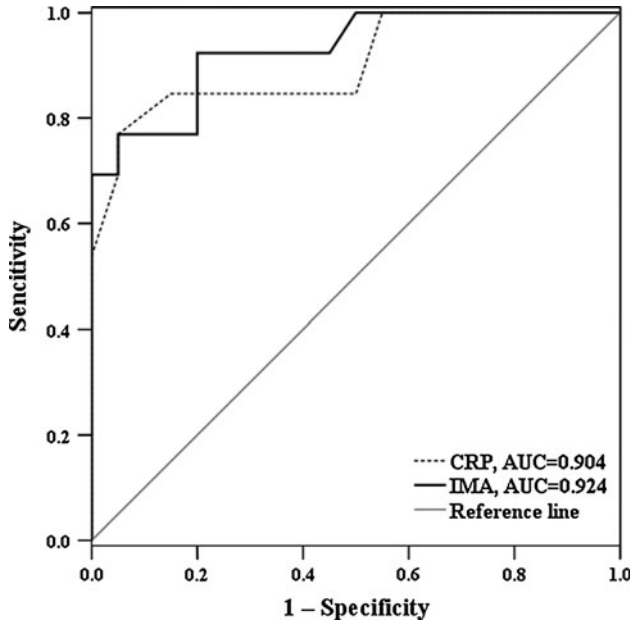

Fig. 3 The AUC for IMA (0.929 ± 0.053) and CRP (0.904 ± 0.061). ROC plots show no difference in the ability of serum CRP and IMA levels to diagnose the presence of DKA. The optimum diagnostic cut-off for IMA was 79.67 U/L (for a sensitivity and specificity of 81.2 and 89.5 %, respectively). For CRP, this point was 4.0 mg/L (for a sensitivity and specificity of 64.7 and 95.5 %, respectively)

CRP levels were significantly elevated in patients with DKA compared with non-DKA and control subjects. To a certain degree, IMA levels were correlated with the severity of DKA. Treatment with insulin reduced CRP and IMA levels and had a favorable effect on the patient's glycemic control. Statistical analysis showed that elevated IMA levels can be a risk marker for DKA and is sensitive in distinguishing from DKA. The measurement of IMA has such advantages as lower price and more convenient application than CRP according on the technical side.

DKA is an acute complication of poorly controlled or newly diagnosed T1D. The pathophysiology of DKA, however, remains unclear. It has been noted that the acute hyperglycemia of DKA is a pro-inflammatory state. It is likely that the pathophysiology of DKA involves some degree of cellular network or capillary perturbation, suggesting a possibly active systemic inflammatory process [18]. Stentz et al. [16] concluded that DKA was associated with the elevation of pro-inflammatory cytokines, reactive oxygen species (ROS), and cardiovascular risk factors. On admission of patients with DKA to the present study, increased CRP and IMA levels were observed. There was positive correlation between CRP and IMA levels and between IMA and plasma glucose levels in the cases with diabetes. We concluded that the albumin molecule in plasma of diabetic patients is modified in the conditions of hyperglycemia, ketoacidosis, oxidative stress, and inflammation, resulting in higher IMA levels. Higher CRP and IMA concentrations were found in patients with moderate/severe DKA than in those with mild DKA, suggesting a correlation among the CRP and IMA levels and the severity degree of DKA. The CRP and IMA levels were reduced or returned to normal within 120 h after the commencement of insulin therapy. The insulin therapy resulted in an anti-inflammatory effect [19].

In a more systematic study in T1D, a variety of markers of oxidative stress were investigated, including glutathione, glutathione peroxidase [20], advanced oxidation protein products [21], and ROS-modified IgG [22]. After 2 h of hyperglycemia, markers of endothelial dysfunction and interleukin (IL)-6 and IL-18 were increased differently depending on the time since diabetes diagnosis. Levels of the oxidative stress markers were normalized by treatment with vitamin C and insulin. Patients who have a different time since diagnosis of T1D react identically to acute hyperglycemia and insulin but differently in regard to glucose normalization [23].

DKA is an inflammatory state associated with the immune response in polymorphonuclear cells. The activation of a subgroup of T-lymphocytes leads to the increased production of ROS and subsequently to increased levels of cytokines and the emergence of growth factor receptors [24]. The identification of the pro-inflammatory cytokines and oxidative stress markers in the hyperglycemic crisis of DKA is of clinical importance. CRP levels are increased in patients with diabetes and DKA, and CRP may serve as a marker for systemic inflammatory response syndrome [10]. The present study achieved similar results. Logistic regression and ROC analysis showed that IMA levels may be a more suitable risk marker than CRP for the diagnosis of DKA. Based on the previous literature and our findings, we concluded that DKA is related to decreased oxygen perfusion in the capillary vessels, triggering albumin modification. High IMA levels in patients with DKA may indicate subclinical vascular disease. The microvascular dysfunction is a potential pathophysiological mechanism of DKA complications such as cerebral edema, pulmonary edema, and abdominal pain [25, 26]. The proper resolution of DKA is aimed at avoiding the most dangerous complication of DKA: cerebral edema [27]. Increased oxidative stress is one of pathological mechanisms for diabetic cardiomyopathy [28]. Fortunately, the participants in the present study did not suffer from congestive heart failure and ischemic events. It is important to develop agents that could prevent the development of DKA and T1D. Preimplantation factor administration results in marked prevention in the early-stage of non-obese diabetic murine models [29].

DKA is characterized by varying degrees of depletion of water and electrolytes. The dehydration leads to hypotension and a hyperosmolar state. At the presentation of the symptoms, the magnitude of specific deficit in an individual patient varies depending upon the duration and severity of T1D or DKA [7, 30]. In this study, patients with DKA had a lower blood pressure and higher Osm compared to non-DKA patients and controls. Serum Osm was <320 mmol/L, suggesting no overlap in the features of the hyperglycemic hyperosmolar state and DKA. The success of the treatment is significantly connected to the correct management of rehydration, metabolic acidosis, and electrolyte deficit replacement [30].

In this study, it was found that IMA levels may be utilized as a biomarker for differentiating patients with T1D that do or do not have DKA. The CRP and IMA levels were significantly reduced, and glycemic variables were well controlled. We can, therefore, conclude that ketoacidosis induces changes in the acute-phase response protein and oxidative stress. The number of participants with DKA was too low to allow for statistically significant conclusions to be made regarding differences among the mild, moderate, and severe DKA groups. Future studies are necessary to elucidate whether the IMA concentration could be utilized in clinical monitoring of T1D patients with chronic and acute complications.

In summary, our study confirms the presence of oxidative stress and chronic low-degree inflammation in patients with T1D. DKA can rapidly deteriorate a patient's antioxidant capacity and serum albumin's metal-binding ability. After the evaluation of CRP and IMA levels in this study, it was determined that the measurement of the IMA concentration could be better suited for the diagnosis and monitoring of DKA.

Conflict of interest The authors have no competing interests to declare.

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