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ORIGINAL ARTICLE

Serum Amyloid A, Malnutrition, Relative Hyperglycemia, and the Development of Diabetic Kidney Disease in Type 2 Diabetes

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SUMMARY

Background: **Serum amyloid A (SAA) plays a vital role in the acute-phase response, acting as a cytokine-like protein. Few studies have examined the role of SAA, malnutrition, and the stress hyperglycemia ratio (SHR) in the development of diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (T2DM). This study investigated the relationship between SAA, nutritional indices, SHR, inflammatory biomarkers, and the prevalence of DKD in overweight and non-overweight patients with T2DM.**
Methods: **A total of 245 patients with newly diagnosed T2DM were evaluated. Levels of SAA, C-reactive protein (CRP), hemoglobin A1c (HbA1c), and fasting plasma glucose (FPG) were measured. SHR, controlling nutritional status (CONUT) score, prognostic nutritional index (PNI), systemic inflammatory index (SII), and inflammatory burden index (IBI) were calculated. CONUT scores ≥ 5.0 and 0 - 1 were defined as high and normal CONUT scores, indicating malnutrition and normal nutritional status, respectively.**
Results: **Patients with a high CONUT score had a 2.9-fold higher prevalence of DKD than those with a normal CONUT score. The prevalence of DKD was significantly higher in patients with elevated SAA levels than in those without elevated SAA levels, whereas no significant difference was observed between patients with elevated and non-elevated CRP levels. PNI and CONUT score were more closely correlated with SAA and CRP levels in non-overweight patients with diabetes than in overweight patients with diabetes. Levels of SAA, CONUT score, SII, and IBI were significantly higher in non-overweight patients than in overweight patients. SHR was more strongly associated with DKD prevalence (odds ratio: 2.471; 95% confidence interval, 1.164 - 5.746; $p < 0.001$) than either HbA1c or FPG. Inflammation combined with malnutrition significantly increased the risk of DKD compared with inflammation or malnutrition alone.**
Conclusions: **Low nutritional status plays a crucial role in the development of DKD, possibly in connection with systemic inflammation, particularly in non-overweight patients with T2DM. SAA and SHR are more closely associated with DKD risk than CRP and HbA1c in patients with diabetes.**
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KEYWORDS

diabetes mellitus, malnutrition, inflammation, diabetic kidney disease

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease that can lead to microvascular and macrovascular complications [1]. Chronic kidney disease (CKD) occurs in 30 - 40% of patients with T2DM and represents a typical form of microvascular complication [2]. Diabetic kidney disease (DKD), previously known as diabetic nephropathy, is the most common CKD and the leading cause of end-stage renal disease (ESRD), accounting for more than 50% of all ESRD cases. Patients with DKD, even in its early stages, have a significantly higher risk of cardiovascular disease [3].

Systemic inflammation plays a pivotal role in the progression of DKD in patients with diabetes. Inflammation enhances reactive oxygen species production, leading to mitochondrial dysfunction, which causes β-cell damage and worsens T2DM [4]. Moreover, inflammation contributes to the deterioration of kidney function. Serum amyloid A (SAA) is an acute-phase protein mainly synthesized in hepatocytes and adipose tissues, with levels that can rapidly increase up to 1,000-fold within the first 24 hours of inflammation [5]. SAA is involved in obesity, acting as a proinflammatory adipokine, and its levels vary with nutritional status [6].

T2DM is characterized by low-grade chronic inflammation, often accompanied by malnutrition and immune disorders [7]. Several nutritional indices, such as the prognostic nutritional index (PNI) and controlling nutritional status (CONUT) score, have been used to assess nutritional status. PNI is a novel marker for immunonutrition that reflects nutritional status, immune function, and chronic inflammation [8]. The CONUT score is a comprehensive tool that easily evaluates malnutrition in hospitalized patients using routine biochemical tests. A CONUT score ≥ 5.0 is generally regarded as indicative of malnutrition [9]. Additionally, the systemic immune-inflammation index (SII) is an integrated biomarker of immunity and inflammation and acts as a risk factor for protein-energy loss in patients with DKD [10].

Stress-induced hyperglycemia commonly occurs in patients with critical illness and leads to impaired glucose metabolism, insulin resistance, and inflammatory reactions [11]. Isolated blood glucose levels at the time of hospital visits do not accurately reflect the overall hyperglycemic state. The stress hyperglycemia ratio (SHR) is a simple and convenient marker for evaluating stress-induced hyperglycemia. SHR is defined as the ratio of fasting plasma glucose (FPG) to estimated average glucose (eAG), accurately reflecting relative hyperglycemia. It is considered a better biomarker in critical illness for identifying patients at higher risk [12]. One study reported that SHR was significantly associated with all-cause and cardiovascular mortality in patients with T2DM [13].

Extensive research has explored the relationship between T2DM, overnutrition, and lifestyle-related factors in individuals with obesity. However, few studies have closely examined the differences in SAA levels, nutritional indices, SHR, and the incidence of DKD between overweight and non-overweight patients with T2DM. Therefore, this study investigated the relationship between SAA, PNI, CONUT score, SHR, SII, and the prevalence of DKD in overweight and non-overweight patients with T2DM. The study also evaluated the effect of malnutrition and relative hyperglycemia on the development of DKD in patients with T2DM.

MATERIALS AND METHODS

Subjects

This study was conducted on 245 patients (140 men and 105 women) with newly diagnosed T2DM who had no history of antihyperglycemic therapy. Patients' ages ranged from 45 to 81 years (mean age: 68.3 years). Age- and gender-matched healthy individuals (n = 125) without evidence of diabetes, inflammation, medication use, or renal dysfunction were enrolled as the control group. T2DM was diagnosed based on the American Diabetes Association criteria [14]. Diabetic kidney disease (DKD) was defined as the presence of elevated urinary albumin excretion (albumin/creatinine ratio [ACR] > 30 μg/mg), decreased estimated glomerular filtration rate (eGFR < 60 mL/minute/1.73 m^2), or both in patients with T2DM [15]. The following subjects were excluded from the study: 1) those with thyroid disease; 2) those with a history of recent surgery, acute blood loss, or transfusion; 3) those with tumors or current pregnancy; and 4) those who had fasted for less than 8 hours. Overweight and non-overweight status were defined as body mass index (BMI) ≥ 23.0 kg/m^2 and BMI < 23.0 kg/m^2, respectively, based on the World Health Organization (WHO) criteria for Asian populations [16]. Information on smoking habits was obtained. The study was approved by the Institutional Review Board of Inha University Hospital (approval number: 2025-02010), and informed consent was obtained from participants. This study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Measurement of laboratory parameters

SAA was measured using a latex turbidimetric immunoassay with human SAA protein detection kits (Medical System Biotechnology Co., Ltd., Ningbo, China). The cutoff level for SAA was defined as 10 mg/L, according to the manufacturer's instructions. The HbA1c fraction was measured via high-performance liquid chromatography using a G8 Glycohemoglobin Analyzer (Tosoh Bioscience, Tokyo, Japan). FPG, serum creatinine, urine albumin, urine creatinine (uCr), thyroid hormones, and liver function tests were analyzed using a chemical analyzer (Cobas 8000 C702; Roche Diagnostics, Mannheim, Germany). ACR was calculated using the following formula: ACR (μg/mg) = [urine albumin (μg/mL)/ μCr (mg/dL)] × 100 [17]. Microalbuminuria, macroalbuminuria, and normoalbuminuria were defined as ACR of 30 - 300 μg/mg, > 300 μg/mg, and < 30 μg/mg, re-

spectively [18]. C-reactive protein (CRP) levels were measured using the highly sensitive CRP kit on the Cobas 8000 analyzer (Roche Diagnostics, Mannheim, Germany). Erythrocyte sedimentation rate (ESR) was determined using the Westergren sedimentation technique with the StaRRsed Auto-Compact (Mechatronics Manufacturing BV, Zwaag, Netherlands). Corrected ESR (cESR) was calculated using the following formula: cESR = (patient's hematocrit/45) × ESR (mm/hour). Elevated CRP and cESR levels were defined as > 0.5 mg/dL and > 15 mm/hour, respectively [19], and considered indicative of systemic inflammation. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula [20].

Calculation of CONUT score, PNI, SII, IBI, eAG, and SHR

The CONUT score was determined by summing the scores assigned based on serum albumin levels, total cholesterol levels, and lymphocyte counts. High CONUT scores (≥ 5) and normal CONUT scores (0 - 1) were defined as indicative of malnutrition and normal nutritional status, respectively [21]. PNI was calculated as follows: PNI = serum albumin (g/dL) × 10 + lymphocyte count (/mm³) × 0.005. Low PNI was defined as < 40 [22]. Inflammation-related biomarkers were calculated as follows: inflammatory burden index (IBI) = CRP (mg/dL) × neutrophil count (/mm³)/lymphocyte count (/mm³) [23], and SII = neutrophil count (/mm³) × platelet count/lymphocyte count (/mm³) [24]. Estimated average glucose (eAG) was calculated using: eAG (mmol/L) = 1.59 × HbA1c (%) - 2.59 [25]. SHR was calculated as: SHR = FPG (mmol/L)/eAG (mmol/L) [26].

Categorization of subjects

Patients were categorized into the following groups: those with DKD (n = 62) and without DKD (n = 183); those with malnutrition (CONUT score ≥ 5.0; n = 91) and with normal nutrition (CONUT score 0 - 1; n = 70); and overweight patients with T2DM (BMI ≥ 23.0 kg/m^2; n = 180) and non-overweight patients with T2DM (BMI < 23.0 kg/m^2; n = 65). Additional stratification was based on the following parameters: SAA levels: high (> 10 mg/L; n = 142) and low (≤ 10 mg/L; n = 103); CRP levels: elevated (> 0.5 mg/dL; n = 134) and non-elevated (≤ 0.5 mg/dL; n = 111); and PNI: low (< 40; n = 92) and high (≥ 40; n = 153).

Statistical analysis

Data were expressed as mean ± standard deviation (SD), median (interquartile range [IQR]), or frequencies (percentages). Differences in means between two groups were analyzed using Student's *t*-test for normally distributed continuous variables and the Mann-Whitney U-test for non-normally distributed variables. Normality was assessed using the Shapiro-Wilk test. Categorical variables were analyzed using the χ^2 test. Multivariate linear regression analysis was used to assess the relationship between nutritional indices and glycemic parameters, with adjustment for potential confounders, including age, gender, systolic blood pressure (SBP), body mass index (BMI), alanine aminotransferase (ALT), and smoking habits. The relationships among nutritional status, inflammatory biomarkers, glycemic parameters, and the prevalence of DKD were evaluated using multivariate logistic regression analysis. The predictive ability of PNI, SAA, CRP, and HbA1c for identifying DKD was assessed using receiver operating characteristic (ROC) curve analysis. Statistical analyses were performed using SPSS (version 26; IBM SPSS Statistics, Armonk, NY, USA) and MedCalc (version 20; MedCalc Software Ltd., Ostend, Belgium). A p-value < 0.05 was considered statistically significant.

RESULTS

Clinical and laboratory characteristics of patients

Out of the 245 patients, 62 (25.3%) had DKD, 97 (39.6%) had systemic inflammation, and 91 (37.1%) had malnutrition based on CONUT score. Compared to overweight patients with T2DM, non-overweight patients with T2DM had significantly higher CONUT scores and significantly lower PNI (5.31 and 34.5 versus 3.54 and 40.3, respectively; p < 0.001). SAA, SII, IBI, and CRP levels were significantly higher in non-overweight patients than in overweight patients. In contrast, no significant differences were observed in FPG, HbA1c, DKD prevalence, eGFR, or glycosuria between the two groups (Table 1). CONUT scores in patients with T2DM and in healthy individuals are shown in Figure 1.

CONUT scores and SAA levels in patients with DKD

CONUT scores and SAA levels were significantly higher in patients with DKD than in those without DKD. Compared to patients without DKD, patients with DKD had a 1.6-fold and 1.5-fold higher prevalence of systemic inflammation and malnutrition, respectively. FPG levels were significantly higher in patients with DKD than in those without DKD (197.4 mg/dL versus 165.2 mg/dL, p < 0.001), whereas no significant difference was noted in HbA1c levels between the two groups (Table 2). CONUT scores and PNI values in patients with and without DKD are illustrated in Figure 2.

DKD and inflammation indices according to nutritional status

DKD and inflammatory indices were analyzed based on nutritional status. DKD was three times more prevalent in patients with high CONUT scores than in those with normal CONUT scores (34.1% versus 11.4%, p < 0.001). The prevalence of non-overweight T2DM was 4.1 times higher in patients with high CONUT scores than in those with normal scores. Levels of SAA, CRP, SII, and IBI were significantly higher in patients with

Table 1. Clinical and laboratory characteristics of patients.

Parameters	Patients with T2DM			p-value *
	total (n = 245)	overweight (n = 180)	non-overweight (n = 65)	
Clinical characteristics				
Age (years)	68.3 ± 13.4	68.1 ± 13.7	70.6 ± 13.2	0.205
Gender (male, n, %)	140 (57.1)	100 (55.6)	40 (61.5)	0.412
BMI (kg/m^2)	24.0 ± 4.5	26.8 ± 3.6	19.9 ± 2.1	< 0.001
SBP (mmHg)	132.0 ± 24.9	133.8 ± 24.5	129.4 ± 25.6	0.328
DBP (mmHg)	77.5 ± 15.4	78.5 ± 12.1	76.0 ± 19.2	0.372
Current smoking (n, %)	53 (21.6)	40 (22.2)	13 (20.0)	0.713
Disease duration (years)	1.3 ± 0.8	1.4 ± 0.9	1.2 ± 0.7	0.106
Nutritional indices				
PNI	38.8 ± 6.4	40.3 ± 5.6	34.5 ± 6.4	< 0.001
CONUT score	4.01 ± 2.32	3.54 ± 2.11	5.31 ± 2.43	< 0.001
Malnutrition (n, %)	91 (37.1)	54 (30.0)	37 (56.9)	< 0.001
Glycemic parameters				
FPG (mg/dL)	173.4 ± 65.1	171.7 ± 62.6	178.2 ± 73.8	0.495
HbA1c (%)	6.91 ± 0.52	6.95 ± 0.53	6.81 ± 0.47	0.061
Inflammatory biomarkers				
SAA (mg/L)	105.4 (13.1 - 216.2)	12.7 (3.9 - 124.5)	116.7 (6.8 - 239.5)	< 0.001
SII	847.3 (431.4 - 1,927.5)	702.1 (385.7 - 1,632.5)	1,318.2 (602.9 - 3,276.5)	< 0.001
IBI	3.1 (0.3 - 40.6)	1.5 (0.2 - 24.3)	17.6 (1.9 - 87.3)	< 0.001
CRP (mg/dL)	0.76 (0.14 - 6.13)	0.45 (0.12 - 3.78)	3.13 (0.35 - 10.62)	< 0.001
Systemic inflammation (n, %)	97 (39.6)	63 (35.0)	34 (52.3)	0.014
Renal parameters				
DKD (n, %)	62 (25.3)	42 (23.3)	20 (30.8)	0.235
eGFR (mL/minute/1.73 m^2)	79.5 ± 27.3	78.4 ± 23.6	82.6 ± 35.4	0.287
Glycosuria (n, %)	63 (25.7)	45 (25.0)	18 (27.7)	0.671

*** Overweight patients with T2DM were compared with non-overweight patients with T2DM.**
Data are expressed as mean ± SD, median (IQR), or frequency (%).
BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, PNI prognostic nutritional index, CONUT controlling nutritional status, FPG fasting plasma glucose, HbA1c hemoglobin A1c, SAA serum amyloid A, SII systemic immune-inflammation index, IBI inflammatory burden index, CRP C-reactive protein, DKD diabetic kidney disease, eGFR estimated glomerular filtration rate, T2DM type 2 diabetes mellitus.

high CONUT scores compared to in patients with normal CONUT scores. In contrast, no significant differences in HbA1c or FPG levels were observed between the two groups (Table 3).

Prevalence of DKD in relation to SAA and CRP levels

The prevalence of DKD was significantly higher in patients with elevated SAA levels than in those with non-elevated SAA levels (30.3% versus 18.4%, p = 0.034). However, no significant difference in DKD prevalence was found between patients with elevated and non-elevated CRP levels (Table 4).

Relationship between SAA, CRP, and nutritional indices

After adjusting for potential confounders, SAA levels were more strongly correlated with CRP levels in overweight patients with T2DM (r = 0.819) than in non-overweight patients with T2DM (r = 0.692). In contrast, CRP levels were more strongly correlated with PNI and CONUT score in non-overweight patients with T2DM than in overweight patients with T2DM (Table 5). Scatter plots depicting the relationships between CRP, SAA, PNI, and CONUT score are presented in Figure 3.

Table 2. Nutritional indices, glycemic parameters, and inflammatory biomarkers in patients with and without DKD.

Parameters	Patients with T2DM		p-value
	with DKD (n = 62)	without DKD (n = 183)	
Anthropometric parameters			
Age (years)	69.5 ± 12.7	68.1 ± 13.4	0.472
Gender (male, n, %)	39 (62.9)	101 (55.2)	0.291
BMI (kg/m^2)	24.1 ± 4.6	23.9 ± 4.5	0.763
SBP (mmHg)	140.2 ± 30.3	128.7 ± 21.8	0.018
DBP (mmHg)	77.4 ± 12.9	77.5 ± 16.5	0.994
Nutritional indices			
PNI	36.7 ± 5.3	39.4 ± 6.5	0.004
CONUT score	4.74 ± 2.11	3.75 ± 2.34	0.003
Malnutrition (n, %)	31 (50.0)	60 (32.8)	0.015
Glycemic parameters			
FPG (mg/dL)	197.4 ± 77.2	165.2 ± 59.3	< 0.001
HbA1c (%)	6.94 ± 0.48	6.90 ± 0.52	0.594
T2DM (n, %)			
Overweight patients with T2DM	42 (67.7)	138 (75.4)	0.236
Non-overweight patients with T2DM	20 (32.3)	45 (24.6)	0.236
Inflammatory biomarkers			
SAA (mg/L)	152.3 (5.8 - 271.2)	74.6 (3.9 - 148.1)	< 0.001
SII	1,071.5 (506.5 - 2,143.1)	758.2 (399.5 - 1,865.2)	0.276
IBI	6.8 (1.2 - 70.4)	2.2 (0.3 - 35.6)	0.039
CRP (mg/dL)	1.21 (0.20 - 8.23)	0.71 (0.12 - 7.15)	0.054
cESR (mm/hour)	37.9 ± 24.1	25.0 ± 17.3	0.002
Systemic inflammation (n, %)	34 (54.8)	63 (34.4)	0.005
Renal parameters			
eGFR (mL/minute/1.73 m^2)	50.3 ± 9.6	89.4 ± 24.1	< 0.001
Glycosuria (n, %)	22 (35.5)	41 (22.4)	0.041

Data are expressed as mean ± SD, median (IQR), or frequency (%).
BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, PNI prognostic nutritional index, CONUT controlling nutritional status, FPG fasting plasma glucose, HbA1c hemoglobin A1c, T2DM type 2 diabetes mellitus, SII systemic immune-inflammation index, IBI inflammatory burden index, SAA serum amyloid A, CRP C-reactive protein, cESR corrected erythrocyte sedimentation rate, eGFR estimated glomerular filtration rate, DKD diabetic kidney disease.

Odds ratio for the prevalence of DKD

The associations between SHR, inflammation, glycemic parameters, nutritional status, and the prevalence of DKD were analyzed using multivariate logistic regression. SHR was more strongly associated with DKD prevalence (odds ratio: 2.471; 95% confidence interval [CI], 1.164 - 5.746; $p < 0.001$) than either HbA1c or FPG. The presence of both inflammation and malnutrition significantly increased the odds ratio for DKD compared with the presence of either condition alone (odds ratio: 2.153; 95% CI, 1.132 - 4.092, $p < 0.001$ versus 1.219; 95% CI, 1.016 - 2.654, $p = 0.003$ and 1.205; 95% CI, 1.012 - 2.598, $p = 0.006$) (Table 6).

Ability of PNI, CONUT score, and glycemic parameters to identify DKD

The diagnostic performance of nutritional indices, inflammatory biomarkers, and glycemic parameters in identifying DKD was assessed using ROC curve analysis. The areas under the curves (AUCs) for PNI, CONUT score, and FPG were significantly larger than that for HbA1c (AUCs: 0.717; 95% CI, 0.643 - 0.791; 0.683; 95% CI, 0.605 - 0.761; and 0.659; 95% CI, 0.561 - 0.756 versus 0.540; 95% CI, 0.449 - 0.630, respectively; $p < 0.05$). In contrast, the AUCs of SAA and CRP were not significantly different from that of HbA1c (Figure 4).

Table 3. DKD and inflammatory indices according to the nutritional status based on CONUT scores.

Parameters	Nutritional status		p-value
	malnutrition (CONUT score ≥ 5.0; n = 91)	normal nutrition (CONUT score: 0 - 1; n = 70)	
Anthropometric parameters			
Age (years)	69.5 ± 12.8	66.2 ± 12.5	0.103
Gender (male, n, %)	58 (63.7)	38 (54.3)	0.229
BMI (kg/m^2)	24.0 ± 5.2	24.2 ± 3.6	0.895
SBP (mmHg)	129.2 ± 25.1	139.5 ± 27.8	0.165
DBP (mmHg)	75.3 ± 17.7	84.6 ± 13.2	0.060
T2DM (n, %)			
Overweight patients with T2DM	54 (59.3)	63 (90.0)	< 0.001
Non-overweight patients with T2DM	37 (40.6)	7 (10.0)	< 0.001
Glycemic parameters			
FPG (mg/dL)	172.0 ± 60.7	159.8 ± 64.3	0.218
HbA1c (%)	6.82 ± 0.45	6.90 ± 0.56	0.343
Kidney function			
DKD (n, %)	31 (34.1)	8 (11.4)	< 0.001
eGFR (mL/min/1.73 m^2)	76.5 ± 33.1	82.5 ± 20.1	0.034
Albuminuria (n, %)	17 (18.7)	2 (2.9)	0.002
Glycosuria (n, %)	26 (28.6)	8 (11.4)	0.008
Inflammatory indices			
SAA (mg/L)	192.1 (32.4 - 267.5)	4.2 (3.9 - 10.6)	< 0.001
SII	2,048.5 (1,002.9 - 3,782.1)	440.8 (332.1 - 708.6)	< 0.001
IBI	48.5 (8.5 - 136.9)	0.29 (0.11 - 0.92)	< 0.001
CRP (mg/dL)	5.97 (1.06 - 13.91)	0.15 (0.07 - 0.51)	< 0.001
Systemic inflammation (n, %)	56 (61.5)	8 (11.4)	< 0.001

Data are expressed as mean ± SD, median (IQR), or frequency (%).
BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, T2DM type 2 diabetes mellitus, FPG fasting plasma glucose, HbA1c hemoglobin A1c, DKD diabetic kidney disease, eGFR estimated glomerular filtration rate, SAA serum amyloid A, SII systemic immune-inflammation index, IBI inflammatory burden index, CRP C-reactive protein, CONUT controlling nutritional status.

Table 4. Prevalence of DKD in relation to inflammatory biomarkers and nutritional indices.

Parameters	Prevalence of DKD		
	subjects (n)	DKD (n, %)	p-value
Inflammatory biomarkers			
SAA (mg/L)			
> 10	142	43 (30.3)	0.034
≤ 10	103	19 (18.4)	
CRP (mg/dL)			
> 0.5	134	39 (29.1)	0.132
≤ 0.5	111	23 (20.7)	
Nutritional indices			
PNI			
≥ 40	153	32 (20.9)	0.041
< 40	92	30 (32.6)	

Data are expressed as frequency (%).
SAA serum amyloid A, CRP C-reactive protein, PNI prognostic nutritional index, DKD diabetic kidney disease.

Table 5. Correlation between SAA, CRP, nutritional indices, and inflammatory biomarkers in overweight and non-overweight patients with T2DM.

Parameters	Multivariate regression analysis *			
	SAA		CRP	
	standardized β	p-value	standardized β	p-value
In non-overweight T2DM				
Nutritional indices				
PNI	-0.409	< 0.001	-0.515	< 0.001
CONUT score	0.476	< 0.001	0.505	< 0.001
Inflammatory biomarkers				
SII	0.242	0.117	0.250	0.115
IBI	0.455	< 0.001	0.619	< 0.001
CRP	0.692	< 0.001	NA	NA
cESR	0.439	< 0.001	0.452	< 0.001
In overweight T2DM				
Nutritional indices				
PNI	-0.332	0.005	-0.398	< 0.001
CONUT score	0.373	0.001	0.302	0.010
Inflammatory biomarkers				
SII	0.268	< 0.001	0.270	0.009
IBI	0.490	< 0.001	0.747	< 0.001
CRP	0.819	< 0.001	NA	NA
cESR	0.504	< 0.001	0.490	< 0.001

* Adjusted for age, gender, SBP, BMI, ALT, and smoking habits.
T2DM type 2 diabetes mellitus, PNI prognostic nutritional index, CONUT controlling nutritional status, SII systemic immune-inflammation index, IBI inflammatory burden index, CRP C-reactive protein, cESR corrected erythrocyte sedimentation rate, SAA serum amyloid A, NA not applicable.

Table 6. Association between SHR, CONUT scores, inflammation, and the prevalence of DKD in patients with T2DM.

Parameters	Prevalence of DKD *	
	odds ratio (95% CI)	p-value
Glycemic parameters [a]		
FPG	1.075 (1.005 - 1.128)	0.016
HbA1c	1.023 (0.781 - 1.209)	0.382
SHR	2.471 (1.164 - 5.746)	< 0.001
Nutritional indices		
CONUT score	1.073 (1.008 - 1.145)	0.019
PNI	1.035 (1.002 - 1.096)	0.027
Inflammatory biomarkers		
SAA	1.018 (1.001 - 1.173)	0.031
CRP	1.010 (0.952 - 1.149)	0.098
Inflammation and malnutrition		
Inflammation alone	1.219 (1.016 - 2.654)	0.003
Malnutrition alone	1.205 (1.012 - 2.598)	0.006
Both inflammation and malnutrition	2.153 (1.132 - 4.092)	< 0.001

* Adjusted for age, gender, SBP, BMI, ALT, and smoking habits.
[a] Adjusted for age, gender, SBP, BMI, ALT, smoking habits, CONUT scores, and CRP.
FPG fasting plasma glucose, HbA1c hemoglobin A1c, SHR stress hyperglycemia ratio, CONUT controlling nutritional status, PNI prognostic nutritional index, SAA serum amyloid A, CRP C-reactive protein, DKD diabetic kidney disease, CI confidence interval.

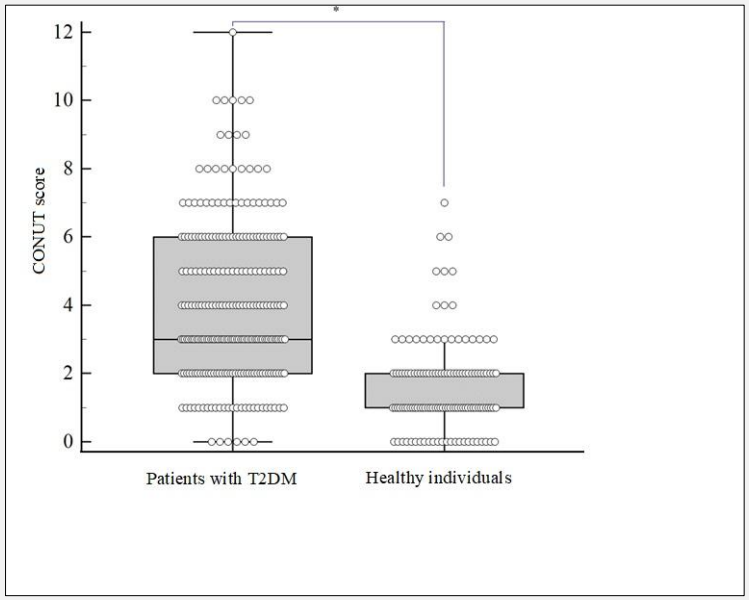

Figure 1. Dot plots showing CONUT scores in patients with T2DM and healthy individuals.

CONUT scores are significantly higher in patients with T2DM than in healthy individuals (4.01 versus 1.72). * p < 0.001.
CONUT controlling nutritional status, T2DM type 2 diabetes mellitus.

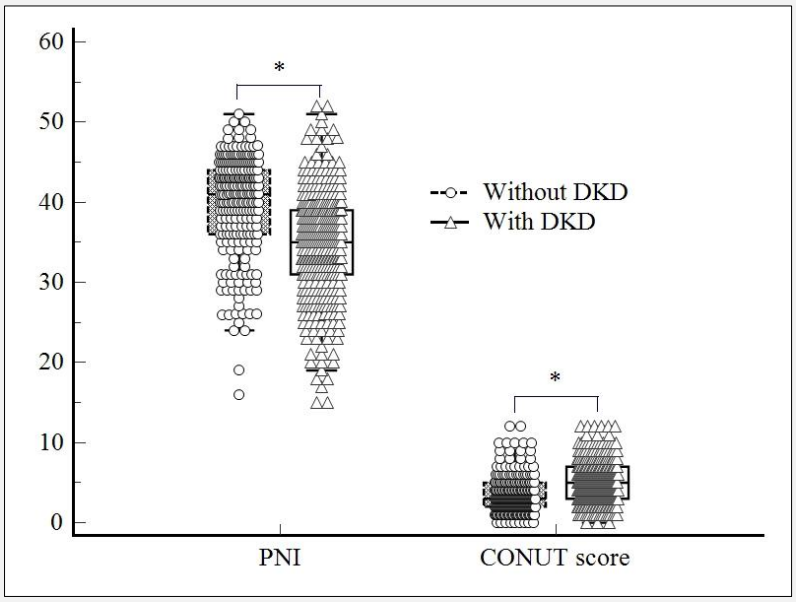

Figure 2. CONUT scores and PNI in patients with and without DKD.

Patients with DKD exhibit significantly higher CONUT scores and significantly lower PNI than patients without DKD (4.74 and 36.7 versus 3.75 and 39.4, respectively). * p < 0.001.
CONUT controlling nutritional status, PNI prognostic nutritional index, DKD diabetic kidney disease.

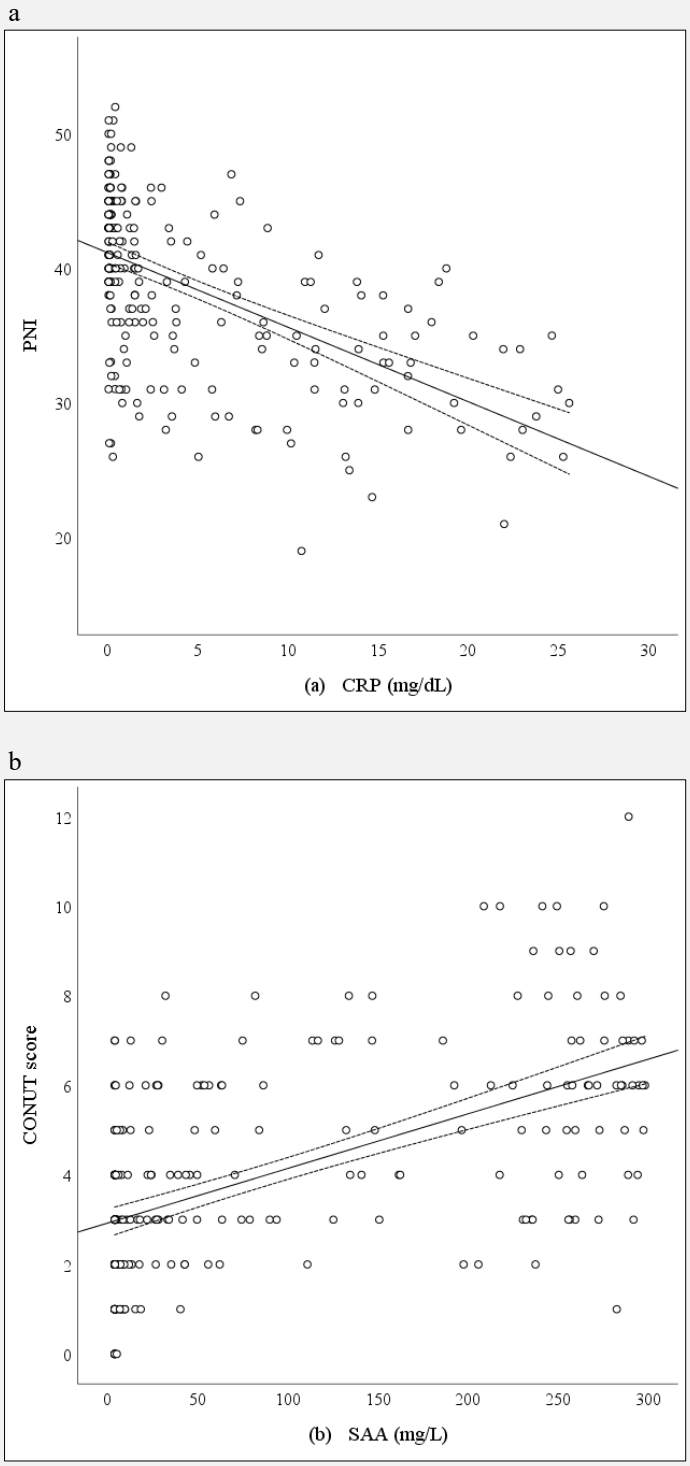

Figure 3. Scatter plots showing the relationships between SAA, CRP, PNI, and CONUT scores.

CRP and SAA levels are significantly correlated with PNI (a) and CONUT scores (b) in patients with T2DM, respectively ($y = –0.55x + 41.17$, $r^2 = 0.319$, $p < 0.001$; and $y = 0.01x + 2.92$, $r^2 = 0.315$, $p < 0.001$).
SAA serum amyloid A, CRP C-reactive protein, PNI prognostic nutritional index, CONUT controlling nutritional status, T2DM type 2 diabetes mellitus.

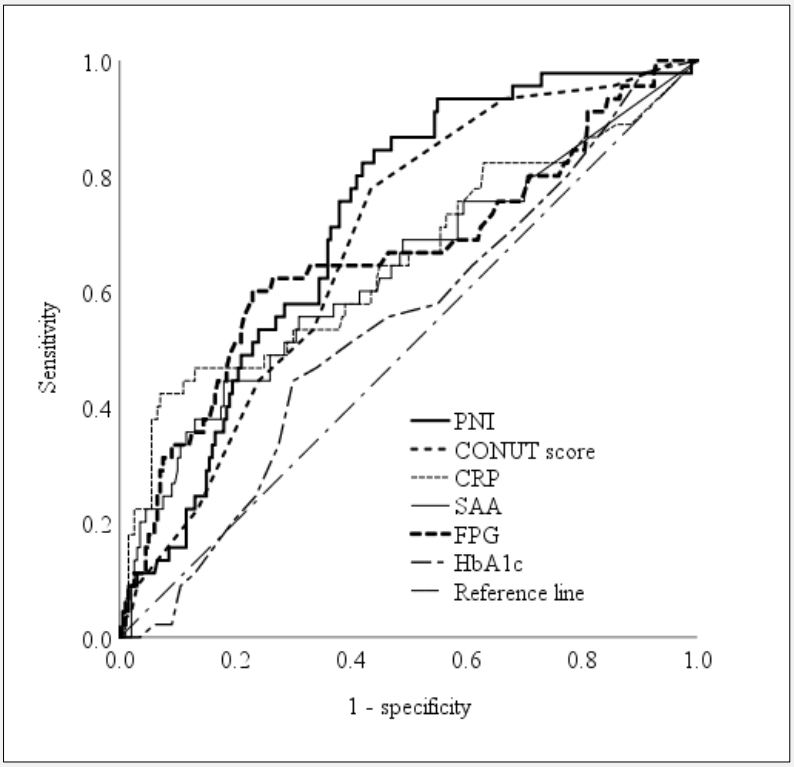

Figure 4. Ability of nutritional indices, inflammatory biomarkers, and glycemic parameters to identify DKD in patients with T2DM.

AUCs for PNI, CONUT scores, and FPG are significantly larger than that for HbA1c (AUCs: 0.717, 95% CI, 0.643 - 0.791; 0.683, 95% CI, 0.605 - 0.761; and 0.659, 95% CI, 0.561 - 0.756 versus 0.540, 95% CI, 0.449 - 0.630, respectively; $p < 0.05$). In contrast, the AUCs of SAA and CRP, which are similar to each other, are not significantly different from that of HbA1c.
DKD diabetic kidney disease, T2DM type 2 diabetes mellitus, AUCs area under the curves, PNI prognostic nutritional index, CONUT controlling nutritional status, FPG fasting plasma glucose, HbA1c hemoglobin A1c, SAA serum amyloid A, CRP C-reactive protein, CI confidence interval.

DISCUSSION

In the present study, the roles of SAA, SHR, and malnutrition in the development of DKD were investigated in overweight and non-overweight patients with T2DM. The main findings are as follows: 1) PNI and CONUT scores outperformed HbA1c in identifying DKD; 2) SHR exhibited a stronger association with the prevalence of DKD than did HbA1c and FPG; 3) SAA levels were significantly higher in non-overweight patients with T2DM than in overweight patients, with a closer association with PNI and CONUT scores; and 4) inflammation with malnutrition more significantly increased the odds ratio for DKD than did inflammation or malnutrition alone.

Malnutrition refers to a condition in which an individual's energy or nutrient intake is insufficient, excessive, or unbalanced [27]. Malnutrition can manifest as overweight, obesity, and sarcopenic obesity [28]. It increases basal inflammation and exaggerates the inflammatory response to sterile tissue injury [29]. Malnutrition also leads to disturbances in the composition of the intestinal microbiome, resulting in a dysbiotic state that triggers inflammatory responses [28]. Indeed, acute malnutrition increases the risk of infection and is closely associated with increased mortality, especially in children under five years of age [29]. On the other hand, inflammation is a major cause of disease-related malnutrition, leading to anorexia, reduced food intake, muscle catabolism, and insulin resistance [30].

In this study, the relationship between malnutrition based on CONUT scores, inflammation, and the prevalence of DKD was evaluated in patients with T2DM. The CONUT score was significantly higher in patients with DKD than in those without DKD. The prevalence of DKD was significantly higher in patients with high

CONUT scores than in those with low CONUT scores. In particular, compared with patients with normal nutritional status, patients with malnutrition exhibited approximately three-fold higher prevalence of DKD. Patients with DKD also had a 1.5-fold higher prevalence of malnutrition than did those without DKD. Additionally, in ROC curve analysis, PNI and CONUT scores were superior to HbA1c in identifying DKD, whereas SAA and CRP did not outperform HbA1c. More importantly, having both malnutrition and inflammation more notably increased the risk for DKD than having malnutrition or inflammation alone. Therefore, it appears that malnutrition and inflammation affect each other's progression, creating a cycle in which malnutrition triggers inflammation, and inflammation supports malnutrition. These results are consistent with a previous study that demonstrated a high CONUT score was associated with a high odds ratio of CKD in patients with T2DM [31]. Overall, these findings indicate that malnutrition is closely associated with the prevalence of DKD and has a more detrimental effect on kidney function in patients with T2DM, especially when combined with systemic inflammation.

Excess body weight is an important risk factor for T2DM; however, people who are not overweight can still be diagnosed with T2DM. The prevalence of non-overweight T2DM has been reported to range from 5% to 18%, with significant differences depending on race: 5.0% in Whites, 10.1% in Asians, 13.5% in Blacks, and 18.0% in Hawaiians [32]. Compared with those who are obese, non-obese individuals with T2DM are characterized by low muscle mass, reduced insulin secretion, and less insulin resistance [33]. In T2DM, chronic low-grade inflammation originating from metabolic cells in response to excess nutrients, known as meta-inflammation or metaflammation, critically contributes to multi-organ dysfunction [34].

In this study, nutritional indices and inflammatory biomarkers were evaluated in non-overweight patients with T2DM compared with overweight patients. Non-overweight patients exhibited significantly higher CONUT scores and significantly lower PNI than did overweight patients. Moreover, the prevalence of non-overweight T2DM was 4.1-fold higher in patients with high CONUT scores than in those with normal CONUT scores. In particular, compared with overweight patients, non-overweight patients exhibited significantly higher levels of inflammation-related biomarkers, such as SAA, SII, IBI, and CRP. Interestingly, CRP was more strongly correlated with SAA in overweight patients than in non-overweight patients, whereas CRP was more closely correlated with PNI and CONUT scores in non-overweight patients. These findings suggest that more severe inflammation in non-overweight patients with T2DM may be due to malnutrition, as indicated by CONUT scores and PNI. Considering these findings, it is likely that factors other than obesity, such as malnutrition and inflammation, may contribute more significantly to the development of T2DM in non-overweight individuals. Collectively, it appears that non-overweight patients with T2DM may be at greater risk than overweight patients, at least in terms of inflammation and nutritional status.

Admission glycemia may not accurately reflect the true hyperglycemic state in patients with T2DM who have chronically elevated blood glucose levels. Recently, SHR has been proposed as a novel index of stress-induced hyperglycemia, reflecting acute blood glucose changes in response to illnesses or injuries [35]. SHR is considered an index of relative hyperglycemia because it is calculated using FPG levels, which reflect acute glycemia, and eAG values, which reflect chronic glycemia. A recent study showed that SHR was significantly associated with unfavorable cardiovascular clinical outcomes and short-term adverse cardiovascular events [36]. In our study, the association between SHR, glycemic parameters, and the prevalence of DKD was evaluated using the odds ratio of DKD. Multivariate regression analysis revealed that SHR was more strongly associated with the presence of DKD than HbA1c and FPG, increasing the odds ratio of DKD by 2.4-fold. This association remained consistent even after adjusting for potential confounders, including CONUT scores and CRP levels. These results suggest that SHR may play an important role as a potential risk factor for the development of DKD in patients with T2DM, regardless of nutritional status and inflammation.

SAA is an acute-phase reactant and plays an important role in both acute and chronic inflammation. SAA induces inflammation and apoptosis in kidney cells and is closely associated with the pathologic changes of DKD [37]. Although SAA and CRP have been widely used as indicators of inflammation, there have been many conflicting results regarding their efficacy in evaluating inflammatory diseases. In some studies, SAA exhibited better performance in assessing systemic inflammation than CRP [38,39]. Additionally, several researchers have demonstrated that SAA is a more sensitive marker than CRP in subclinical and low-grade inflammation [40]. Furthermore, Zhang et al. [41] reported that SAA was more accurate than CRP in assessing patients with viral infections, acute pancreatitis, and rejection reactions to kidney transplants. However, in another study, CRP showed better proficiency than SAA in monitoring crises and attack-free periods in systemic auto-inflammatory diseases [42].

In our study, patients with DKD had significantly higher SAA levels than did those without DKD, with a higher incidence of SAA elevation. However, no significant difference was noted in either CRP levels or the incidence of CRP elevation between the two groups. Moreover, the prevalence of DKD was significantly higher in patients with elevated SAA levels than in those with non-elevated SAA levels. In contrast, no significant difference was found between patients with and without elevated CRP levels. These results suggest that SAA may be more closely related to the development of DKD than CRP in patients with T2DM. These findings

are supported by a study showing that high SAA levels are significantly associated with an increased risk of ESRD and mortality in patients with advanced DKD [37].

This study has several limitations. The sample size of patients with DKD was small, and oral glucose tolerance tests were not performed. This study could not evaluate dietary habits, total energy intake, or alcohol consumption. As this was a cross-sectional observational study, the specific mechanisms underlying the relationship between SAA and T2DM could not be validated. Despite these limitations, to the best of our knowledge, this is the first study to report possible evidence of a link between malnutrition, SAA, relative hyperglycemia, and the development of DKD in patients with T2DM. Further investigation is warranted to verify these findings in larger randomized prospective trials.

In conclusion, this study demonstrates that nutritional status may play a pivotal role in the development of DKD, possibly in connection with systemic inflammation, especially in non-overweight patients with T2DM. The prevalence of DKD was higher in patients with elevated SAA levels but not in those with elevated CRP levels, and SHR more significantly increased the odds ratio for DKD than did HbA1c and FPG. These findings suggest that measuring SAA, SHR, and CONUT scores may be beneficial in monitoring the potential progression of DKD in patients with T2DM.

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Declaration of Interest:

The authors declare that they have no conflicts of interest.

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