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Original Article

Hemoglobin A1c, Not Glycated Albumin, Can Independently Reflect the Ankylosing Spondylitis Disease Activity Score

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Objective. This study examined whether glycated hemoglobin (HbA1c) and glycated albumin (GA) are well correlated with the Ankylosing Spondylitis Disease Activity Score (ASDAS)-erythrocyte sedimentation rate (ESR), and ASDAS-C-reactive protein (CRP) in AS patients without medical conditions affecting the glycated protein levels. **Methods:** The data of 76 patients with AS were analyzed. Univariate and multivariate analyses of the variables associated with ASDAS-ESR and ASDAS-CRP were performed using a linear regression test. The patients were divided into active and inactive AS groups based on an ASDAS-CRP of 2.1, and the variables between the two groups were compared. **Results.** ASDAS-ESR did not correlated with either HbA1c or GA. ASDAS-CRP was positively correlated with HbA1c ($r=0.315$, $p=0.006$) and the white blood cell ($r=0.288$, $p=0.012$), and inversely correlated with hemoglobin ($r=-0.241$, $p=0.036$) and serum albumin ($r=-0.262$, $p=0.022$), but not GA. Multivariate analysis revealed HbA1c and white blood cell to be significantly correlated with ASDAS-CRP ($\beta=0.234$, $p=0.033$ and $\beta=0.265$, $p=0.017$). The mean HbA1c, not GA, of the active group was significantly higher than that of the inactive group ($p=0.020$). In addition, the optimal cut-off value of HbA1c was set to 5.6, and the patients with HbA1c ≥ 5.6 were found to have a 3.3 times higher risk of active AS than those without. **Conclusion.** HbA1c was significantly correlated with ASDAS-CRP, and could be a useful marker to reflect ASDAS-CRP in AS patients without medical conditions affecting the glycated protein levels. **(J Rheum Dis 2018;25:131-139)**

Key Words. Ankylosing spondylitis, Glycated hemoglobin A, Glycosylated serum albumin

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease that has characteristics of both articular and extra-articular manifestations ranging from inflammatory back pain to uveitis [1]. Before the era of biological disease modifying anti-rheumatic drugs (bDMARDs), the primary goal of therapeutic strategies for AS were to reduce pain and improve the daily activity through conventional synthetic DMARDs (csDMARDs). Despite the use of csDMARDs, however, the progression of AS could not easily delayed or modified at all [2]. Meanwhile, bDMARDs can directly quench the inflammatory response of AS, and in turn, it can minimize AS progression at earlier phase and prevent its systemic complications [3]. Thus, if we can precisely assess the disease activity of AS and not miss the proper time to start bDMARDs, we may expect a good prognosis in AS patients.

However, since the entity of AS is mainly characterized by localized inflammation, especially confined to axial joints, there have been discrepancies between conventional inflammatory markers, including erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and the disease activity of AS in a considerable number of patients [4]. In the clinical settings, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the most widely used tool to assess the disease activity of AS for its convenience. But BASDAI has a limitation that it does not include physician's assessment nor objective evidence of inflammation, because it consists of only patient-reported

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items [5]. To complement it, a new composite index, Ankylosing Spondylitis Disease Activity Score (ASDAS), has been suggested. It adds objective laboratory findings including ESR and CRP to patient-reported items (ASDAS-ESR and ASDAS-CRP) [6]. However, so far, there has been no single serum marker to reflect the disease activity of AS.

Glycated proteins, which are produced through non-enzymatic reaction between sugars and free amino groups of proteins, can be formed in diverse pathological or physiological conditions such as diabetes mellitus and inflammation [7,8]. Glycated hemoglobin (HbA1c) and glycated albumin (GA) are glycated proteins and they can identify plasma glucose concentration in different follow-up durations [9,10]. Moreover, HbA1c and GA were recently reported that they could reflect and monitor the inflammatory burdens [11,12]. But there has been no report regarding the association of HbA1c and GA with the disease activity of AS yet. Hence, in this study, we investigated whether glycated proteins, HbA1c and GA, are adjunctive markers to be well correlated with ASDAS-ESR and ASDAS-CRP in AS patients, who had normal laboratory results including HbA1c, GA and fasting glucose, and who had no medical history of abnormal glucose metabolism and other medical conditions affecting glycated protein levels.

MATERIALS AND METHODS

Patients

We consecutively enrolled 94 patients with AS in this study from March 2015 to October 2015 according to the inclusion criteria as follows: (i) patients who fulfilled modified New York criteria for AS [13], and who had been classified at the Division of Rheumatology, Yonsei University College of Medicine, Severance Hospital; (ii) patients who had no medical history which can influence on the turnover of albumin and red blood cell, including other autoimmune diseases other than AS [12], diabetes mellitus [14], thyroid disease [15], nephrotic syndrome [16], chronic liver diseases [17], and haemolytic anaemia [18] identified by 10th revised international classification of diseases; (iii) patients who had never received medications for those diseases searched by the Korean Drug Utilization Review system; (iv) patients who had no concurrent infection and malignancy to enhance acute reactants levels; (v) patients who gave informed consent to their participation; (vi) patients who took clinical assessment by independent physician on the same day of laboratory tests; (vii) patients having laboratory results fulfilling the following criteria: fasting glucose <126 mg/dL, HbA1c $<6.5\%$, platelet count $>150{,}000/mm^3$, creatinine ≤ 1.3 mg/dL or estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration >60 mL/min/1.73 m^2, serum albumin ≥ 3.5 mg/dL, alkaline phosphatase ≤ 115 IU/L, aspartate aminotransferase ≤ 40 IU/L, alanine aminotransferase ≤ 40 IU/L. We excluded 7 of 94 patients due to medical conditions and 11 of the rest due to the laboratory results exceeding normal values. Finally, we included 76 patients with AS in this study. Demographic features included age, gender, smoking history, body mass index (BMI), the follow-up duration and the use of glucocorticoid and anti-tumour necrosis factor agents. This study was approved by the Institutional Review Board of Severance Hospital (no. 4-2015-0802). Informed consent was obtained from all patients.

Laboratory tests and disease activity assessment

HbA1c levels were measured via automated COBAS INTEGRA 800 (Roche Diagnostics, Mannheim, Germany). GA levels were measured using a Hitachi 7600-120 automatic analyser (Hitachi, Tokyo, Japan) and an enzymatic method and an albumin detection reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan). We selected items of laboratory tests, which are routinely performed at each regular visit, as described in Table 1. ASDAS-ESR and ASDAS-CRP were also obtained by the equations as below: $0.08\times$Back Pain$+0.07\times$Duration of Morning Stiffness$+0.11\times$Patient Global$+0.09\times$Peripheral Pain/Swelling$+0.29\times\sqrt{(ESR)}$ for ASDAS-ESR and $0.12\times$Back Pain$+0.06\times$Duration of Morning Stiffness$+0.11\times$Patient Global$+0.07\times$ Peripheral Pain/Swelling$+0.58\times$Ln (CRP$+1$) [6,19]. Also we assessed the disease activity of AS such as BASDAI [5], Bath Ankylosing Spondylitis Functional Index (BASFI) [20], and Bath Ankylosing Spondylitis Patient Global Score (BAS-G) [21].

Statistical analysis

All statistical analyses were conducted using the IBM SPSS package for Windows version 23.0 (IBM Co., Armonk, NY, USA). Continuous variables were expressed as median (interquartile range) or mean±standard deviation. Correlations between variables were determined by the Pearson rank test. Univariate analysis of the association of variables with ASDAS-ESR and ASDAS-CRP was

Table 1. Baseline characteristics of patients with ankylosing spondylitis (n = 76)

Variable	Value
Demographic data	
Age (yr)	39.0 (18.0)
Male gender	58 (76.3)
Follow-up duration (yr)	5.0 (8.5)
Smoking	29 (38.2)
BMI (kg/m^2)	24.0 (5.0)
HLA-B27	60 (78.9)
Syndesmophyte formation	20 (26.3)
Laboratory results	
HbA1c (%)	5.5 (0.4)
GA (%)	12.7 (1.5)
Fasting glucose (mg/dL)	95.5 (12.8)
ESR (mm/h)	19.0 (28.0)
CRP (mg/L)	2.3 (5.9)
Ferritin (mg/dL)	75.5 (70.0)
White blood cell (/mm^3)	7,325.0 (2,580.0)
Hemoglobin (g/dL)	14.9 (2.4)
Platelet × 10^3 (/mm^3)	261.0 (69.5)
Albumin (mg/dL)	4.4 (0.5)
Blood urea nitrogen (mg/dL)	13.9 (4.4)
Creatinine (mg/dL)	0.8 (0.2)
Alkaline phosphatase (IU/L)	70.0 (26.0)
Aspartate aminotransferase (IU/L)	21.0 (8.0)
Alanine aminotransferase (IU/L)	18.0 (17.0)
Total cholesterol (mg/dL)	188.0 (40.5)
High density cholesterol (mg/dL)	53.0 (17.0)
Low density cholesterol (mg/dL)	107.8 (24.4)
Triglyceride (mg/dL)	96.0 (76.0)
Disease activity indexes	
ASDAS-ESR	2.2 (1.5)
ASDAS-CRP	1.8 (1.4)
BASDAI	3.3 (2.4)
BAS-G	3.0 (3.3)
BASFI	1.3 (2.6)
Medications	
Glucocorticoid use	7 (9.2)
Methotrexate use	5 (6.6)
Sulfasalazine use	39 (51.3)
Anti-TNF agents use	27 (35.5)

Values are expressed as median (interquartile range, IQR) or number (%). BMI: body mass index, HLA: human leukocyte antigen, HbA1c: hemoglobin A1c, GA: glycated albumin, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ASDAS: ankylosing spondylitis disease activity score, BASDAI: bath ankylosing spondylitis disease activity index, BAS-G: bath ankylosing spondylitis patient global score, BASFI: bath ankylosing spondylitis disease activity functional index, TNF: tumour necrosis factor.

performed using linear regression test. Standardized correlation coefficient was assessed by a multivariate linear regression test using variables with significant differences on univariate analysis. The chi-square test and Fisher's exact test were used for significant differences of categorical data between the two groups. We used Student's t-test or Mann-Whitney U-test to compare continuous variables between the two groups. p-values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of patients with ankylosing spondylitis

Baseline characteristics are summarized in Table 1. The median age of patients was 39.0 years old (58 men and 18 women), and the median follow-up duration was 8.1 years. Twenty nine of patients (38.2%) had smoking history, and the median BMI was 24.0 kg/m^2. Human leukocyte antigen B27 was detected in 60 patients (79.0%). The median HbA1c, GA and fasting glucose were 5.5%, 12.7% and 95.5 mg/dL, respectively. The median ESR and CRP were 19.0 mm/hour and 2.3 mg/L. The median ASDAS-ERS and ASDAS-CRP were 2.2 and 1.8, and the median BASDAI, BAS-G and BASFI were assessed as 3.3, 3.0 and 1.3, respectively. Seven patients had ever received glucocorticoid and 27 patients had done anti-tumor necrosis factor (TNF) agents.

Correlation of between glycated proteins and disease activity

We evaluated the correlation of HbA1c and GA with the disease activity indices of AS. HbA1c was remarkably correlated with GA, fasting glucose and BMI (r=0.400, r=0.405 and r=0.227, $p<0.005$ for all). HbA1c showed significantly positive correlation with ASDAS-CRP (r=0.315, p=0.006), but not ASDAS-ERS (r=0.220, p=0.560). Also, HbA1c was meaningfully correlated with BASDAI (r=0.226) and BAS-G (r=0.401), but not BASFI (r=0.124). On the other hands, GA exhibited no significant correlation with any disease activity index of AS (Supplementary Table 1).

Univariate and multivariate analyses of ASDAS-ESR and other variables

Univariate linear regression analysis revealed that ASDAS-ESR was positively correlated with white blood cell (r=0.266, p=0.020) and inversely correlated with he-

moglobin (r=−0.414, p<0.001) and serum albumin (r=−0.394, p<0.001). ASDAS-ESR showed a tendency to correlate with Hb1AC, but it was not statistically significant (r=0.220, p=0.056). ASDAS-ESR was not correlated with GA (Table 2). We included HbA1c in multivariate analysis, because its p-value was almost near the statistical significance. However, on multivariate linear regression analysis, only white blood cell and hemoglobin were significantly correlated with ASDAS-ESR (β=0.266, p=0.011 and β=−0.355, p=0.002).

Univariate and multivariate analyses of ASDAS-CRP and other variables

Univariate linear regression analysis discovered that ASDAS-CRP was positively correlated with HbA1c (r=0.315, p=0.006) and white blood cell (r=0.288, p=0.012) and inversely correlated with haemoglobin (r=−0.241, p=0.036) and serum albumin (r=−0.262, p=0.022). ASDAS-CRP was not correlated with GA. On multivariate linear regression analysis, HbA1c and white blood cell were still significantly correlated with ASDAS-CRP (β=0.234, p=0.033 and β=0.265, p=0.017) (Table 3). Also, we analyzed correlation between the use of medi-

Table 2. Univariate and multivariate analysis of ASDAS-ESR and other variables

Variable	Univariate analysis			Multivariate analysis		
	Regression coefficient (crude B)	Correlation coefficient (R= β)	p-value	Standardized β*	95% confidential interval	p-value
Demographic data						
Age (yr)	0.013	0.172	0.136			
Follow-up duration (yr)	−0.002	−0.011	0.923			
BMI (kg/m^2)	0.003	0.013	0.910			
Laboratory results						
HbA1c (%)	0.661	0.220	**0.056**	0.102	−0.298, 0.911	0.316
GA (%)	0.069	0.105	0.368			
Fasting glucose (mg/dL)	0.001	0.011	0.923			
ESR (mm/h)	N/A	N/A	**N/A**			
CRP (mg/L)	0.054	0.448	**<0.001**			
Ferritin (mg/dL)	−0.002	−0.145	0.296			
White blood cell (/mm^3)	0.120	0.266	**0.020**	0.266	0.028, 0.211	**0.011**
Hemoglobin (g/dL)	−0.229	−0.414	**<0.001**	−0.355	−0.316, −0.075	**0.002**
Platelet×10^3 (/mm^3)	0.003	0.206	0.074			
Serum albumin (mg/dL)	−1.187	−0.394	**<0.001**	−0.195	−1.249, 0.075	0.081
Blood urea nitrogen (mg/dL)	0.057	0.223	0.053			
Creatinine (mg/dL)	−0.620	−0.104	0.373			
Alkaline phosphatase (IU/L)	0.009	0.181	0.121			
Aspartate aminotransferase (IU/L)	0.004	0.029	0.805			
Alanine aminotransferase (IU/L)	0.004	0.040	0.734			
Total cholesterol (mg/dL)	0.003	0.109	0.350			
High density cholesterol (mg/dL)	0.005	0.078	0.569			
Low density cholesterol (mg/dL)	−0.001	−0.040	0.765			
Triglyceride (mg/dL)	0.002	0.121	0.366			
Medications						
Glucocorticoid use	0.350	0.106	0.364			
Methotrexate use	−0.056	−0.015	0.901			
Sulfasalazine use	0.385	0.201	0.082			
Anti-TNF agents use	−0.140	−0.070	0.548			

ASDAS: ankylosing spondylitis disease activity score, ESR: erythrocyte sedimentation rate, BMI: body mass index, HbA1c: hemoglobin A1c, GA: glycated albumin, CRP: C-reactive protein, TNF: tumour necrosis factor, N/A: not available. *CRP was not included in multivariate analysis, because CRP is a variable closely correlated with ESR (ASDAS-ESR) in inflammation in order not to confound the interpretation of statistical results.

Table 3. Univariate and multivariate analysis of ASDAS-CRP and other variables

Variable	Univariate analysis			Multivariate analysis		
	Regression coefficient (crude B)	Correlation coefficient (R= β)	p-value	Standardized β*	95% confidential interval	p-value
Demographic data						
Age (yr)	0.013	0.164	0.158			
Follow-up duration (yr)	0.015	0.105	0.367			
BMI (kg/m^2)	0.008	0.032	0.781			
Laboratory results						
HbA1c (%)	0.972	0.315	**0.006**	0.234	0.060, 1.383	**0.033**
GA (%)	0.091	0.135	0.244			
Fasting glucose (mg/dL)	0.004	0.037	0.750			
ESR (mm/h)	0.026	0.477	**<0.001**			
CRP (mg/L)	N/A	N/A	**N/A**			
Ferritin (mg/dL)	−0.003	−0.199	0.150			
White blood cell (/mm^3)	0.133	0.288	**0.012**	0.265	0.022, 0.222	**0.017**
Hemoglobin (g/dL)	−0.137	−0.241	**0.036**	−0.204	−0.248, 0.016	0.084
Platelet×10^3 (/mm^3)	0.002	0153	0.186			
Serum albumin (mg/dL)	−0.811	−0.262	**0.022**	−0.099	−1.030, 0.419	0.404
Blood urea nitrogen (mg/dL)	0.027	0.104	0.373			
Creatinine (mg/dL)	−0.243	−0.040	0.734			
Alkaline phosphatase (IU/L)	0.011	0.212	0.068			
Aspartate aminotransferase (IU/L)	0.015	0.098	0.402			
Alanine aminotransferase (IU/L)	0.014	0.145	0.213			
Total cholesterol (mg/dL)	0.004	0.119	0.307			
High density cholesterol (mg/dL)	−0.012	−0.159	0.246			
Low density cholesterol (mg/dL)	0.002	0.069	0.609			
Triglyceride (mg/dL)	0.004	0.184	0.166			
Medications						
Glucocorticoid use	0.147	0.044	0.707			
Methotrexate use	0.236	0.060	0.604			
Sulfasalazine use	0.349	0.180	0.120			
Anti-TNF agents use	−0.325	−0.161	0.166			

ASDAS: ankylosing spondylitis disease activity score, CRP: C-reactive protein, BMI: body mass index, HbA1c: hemoglobin A1c, GA: glycated albumin, ESR: erythrocyte sedimentation rate, TNF: tumour necrosis factor, N/A: not available. *ESR was not included in multivariate analysis, because ESR is a variable closely correlated with CRP (ASDAS-CRP) in inflammation in order not to confound the interpretation of statistical results.

cations and ASDAS indexes, there was no statistical significance (Tables 2 and 3).

Comparison of variables between patients with active and inactive AS based on ASDAS-CRP >2.1

When patients with AS had ASDAS-CRP >2.1, they can be considered to have high or very high disease activity. Since HbA1c showed a significant correlation with ASDAS-CRP, but not ASDAS-ESR, we divided patients into active (40 patients) and inactive (36 patients) groups, based on ASDAS-CRP >2.1. There were no significant differences in demographic data between the two groups. The mean HbA1c of patients in active group was significantly higher than that of patients in inactive group (5.6 vs. 5.4, p=0.020), but the mean GA did not differ between the two groups (Table 4). Patients in active group showed the higher mean ESR and white blood cell, whereas, than the lower mean hemoglobin and serum albumin than those in inactive group (30.6 vs. 14.3, p<0.001, 8,273.6 vs. 7,088.5, p=0.013, 14.0 vs. 15.0, p=0.008 and 4.3 vs. 4.5, p=0.016, respectively). The mean ASDAS-ESR, BASDAI and BAS-G in active group were significantly higher than those in inactive group. On the other hand, the frequency of glucocorticoid, methotrexate, sulfasalazine and anti-TNF anti-

Table 4. Comparison variables between patients with active and inactive ankylosing spondylitis based on ASDAS-CRP > 2.1

Variable	Inactive AS (n = 40)	Active AS (n = 36)	p-value
Demographic data			
Age (yr)	37.3 ± 11.2	40.8 ± 12.8	0.201
Male gender	34 (85.0)	24 (66.7)	0.061
Follow-up duration (yr)	7.7 ± 6.4	8.0 ± 7.4	0.824
Smoking	14 (35.0)	15 (41.7)	0.055
BMI (kg/m^2)	24.5 ± 4.0	23.9 ± 4.0	0.526
HLA-B27	30 (75.0)	30 (83.3)	0.374
Laboratory results			
HbA1c (%)	5.4 ± 0.3	5.6 ± 0.3	**0.020**
GA (%)	12.7 ± 1.2	13.0 ± 1.7	0.395
Fasting glucose (mg/dL)	97.7 ± 9.8	95.9 ± 9.7	0.414
ESR (mm/h)	14.3 ± 11.7	30.6 ± 18.8	**< 0.001**
CRP (mg/L)	N/A	N/A	N/A
Ferritin (mg/dL)	107.7 ± 69.4	75.3 ± 73.1	0.100
White blood cell (/mm^3)	7,088.5 ± 1,767.6	8,273.6 ± 2,280.8	**0.013**
Hemoglobin (g/dL)	15.0 ± 1.4	14.0 ± 1.9	**0.008**
Platelet × 10^3 (/mm^3)	252.1 ± 45.4	275.6 ± 75.3	0.110
Albumin (mg/dL)	4.5 ± 0.3	4.3 ± 0.3	**0.016**
Blood urea nitrogen (mg/dL)	14.1 ± 3.4	14.9 ± 4.1	0.330
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.551
Alkaline phosphatase (IU/L)	69.1 ± 18.1	74.5 ± 20.3	0.230
Aspartate aminotransferase (IU/L)	20.5 ± 7.1	21.6 ± 5.7	0.442
Alanine aminotransferase (IU/L)	19.7 ± 10.1	21.7 ± 9.5	0.398
Total cholesterol (mg/dL)	189.7 ± 28.3	194.0 ± 31.6	0.534
High density cholesterol (mg/dL)	53.4 ± 8.6	50.7 ± 15.8	0.425
Low density cholesterol (mg/dL)	116.8 ± 31.4	116.3 ± 29.3	0.945
Triglyceride (mg/dL)	95.5 ± 39.3	113.4 ± 49.1	0.129
Disease activity			
ASDAS-ESR	1.8 ± 0.6	3.1 ± 0.8	**< 0.001**
ASDAS-CRP	N/A	N/A	N/A
BASDAI	2.5 ± 1.2	4.5 ± 1.7	**< 0.001**
BAS-G	2.5 ± 1.7	4.7 ± 2.2	**< 0.001**
BASFI	1.7 ± 4.3	2.9 ± 1.8	0.185
Medications			
Glucocorticoid use	2 (5.0)	5 (13.8)	0.181
Methotrexate use	2 (5.0)	3 (8.3)	0.651
Sulfasalazine use	19 (47.5)	20 (55.5)	0.258
Anti-TNF antibody use	16 (40.0)	11 (30.6)	0.390

Values are expressed as mean ± standard deviation or number (%). ASDAS: ankylosing spondylitis disease activity score, CRP: C-reactive protein, AS: ankylosing spondylitis, BMI: body mass index, HLA: human leukocyte antigen, HbA1c: hemoglobin A1c, GA: glycated albumin, ESR: erythrocyte sedimentation rate, BASDAI: bath ankylosing spondylitis disease activity index, BAS-G: bath ankylosing spondylitis patient global score, BASFI: bath ankylosing spondylitis disease activity functional index, TNF: tumour necrosis factor, N/A: not available.

body uses did not show statistically significant difference between the two groups.

On multivariate logistic regression analysis of these significant variables, only white blood cell and hemoglobin were independently associated with high disease activity of AS based on ASDAS-CRP of 2.1 (odds ratio [OR]=1.442, 95% confidential interval [CI]=1.067, 1.947, p=0.017, and OR=0.656, 95% CI=0.456, 0.940, p=0.022). The statistical significance of HbA1c disappeared on multivariate analysis (OR=4.132, 95% CI=0.704, 24.240, p=0.116) (Table 5).

Table 5. Multivariate logistic regression analysis using variables with statistical significance between patients with active and inactive ankylosing spondylitis based on ASDAS-CRP >2.1

Variable	Odds ratio	95% confidence interval	p-value
HbA1c (%)	4.132	0.704, 24.240	0.116
White blood cell (/mm^3)	1.442	1.067, 1.947	0.017
Hemoglobin (g/dL)	0.656	0.456, 0.940	0.022
Albumin (mg/dL)	0.482	0.075, 3.086	0.441

ASDAS: ankylosing spondylitis disease activity score, CRP: C-reactive protein, HbA1c: hemoglobin A1c.

DISCUSSION

Glycated albumin is a clinical marker to predict for coronary artery disease in type 2 diabetes patients, and it is well known as having correlation with high sensitivity-CRP, TNF-alpha, and interleukin-6 level [22]. In the study using bovine serum albumin, it shows that increased advanced glycation end-products which are representative for glycated albumin in diabetic patients upregulate thrombotic responses and deteriorate vessel geometry through constant disturbed shear stress in endothelial cell [23]. Meanwhile, HbA1c is marker to reflect severity of coronary artherosclerosis in non-diabetic individuals, so it has association in lower albumin concentrations, increased concentration of CRP, fibrinogen and white blood cell level, and so on. It is because HbA1c reflects subclinical derangement in glucose metabolism caused by chronic inflammation though it has normal range [24].

In this study, we first investigated whether glycated proteins, HbA1c and GA, are adjunctive markers to be well correlated with ASDAS-ESR and ASDAS-CRP. And we demonstrated that HbA1c was significantly correlated with ASDAS-CRP, and HbA1c could be a useful marker to reflect ASDAS-CRP in AS patients without medical conditions affecting glycated protein levels. Meanwhile, HbA1c had a tendency to correlate with ASDAS-ESR, but it had no statistical significance (p=0.056). In addition, we found that HbA1c was correlated with BASDAI and BAS-G with statistical significance as well, but in the present study, we focused on the ASDAS-ESR and ASDAS-CRP containing objective laboratory results in their equations. In the real clinical settings, a majority of physicians are measuring the levels of acute reactants, such as ESR and CRP, at each visit of patients of AS. However, most of them have no over-credulity to directly apply them to AS patients to reflect the disease activity, due to its low sensitivity and singularity in AS [25]. By contrast, BASDAI, BAS-G and BASFI are not objectively reliable due to their limited subjective items [5]. ASDAS-ESR and ASDAS-CRP are likely to overcome these limitations by adding objective laboratory results to patient-reported forms. In this regard, our study might be valuable in terms of discovering a convenient serum marker to reflect ASDAS-CRP in AS patients, who had normal laboratory results including HbA1c, GA and fasting glucose, and who had no medical history of abnormal glucose metabolism and other medical conditions affecting glycated protein levels.

In our previous study, we consecutively enrolled 205 patients with rheumatoid arthritis (RA) and analysed their data. And we concluded that GA increased along with the disease activity in rheumatoid factor positive RA patients, and furthermore, GA was an independent and potential predictor of active RA, comparable with ESR and CRP [12]. However, in this study, we failed to elucidate that GA was correlated with the disease activity indices of AS. GA is a newly suggested parameter for the status of glucose metabolism, and it has an advantage in that it can reflect the relatively short-term alternations in plasma glucose concentration, compared to HbA1c, whereas, HbA1c can reflect the status of glucose metabolism over 60 days ago [9,10,26]. In addition, the disease progression and the fluctuation of inflammatory burdens of RA are more changeable than those of AS due to its low sensitivity in AS diagnosis and disease activity assessment [25,27]. Our results also demonstrated that HbA1c was not correlated with CRP (r=0.023, p=0.842) and ESR (r=0.201, p=0.081). But HbA1c was well correlated with ASDAS-CRP, which can reflect the accumulative outcome of the alteration in inflammatory burdens over time. In this regard, we first revealed that HbA1c can reflect subtle impaired glucose tolerance and metabolic alterations provoked by subclinical inflammatory burdens more clearly than GA in patients with AS, unlike RA.

Although there was no statistical significance on multi-

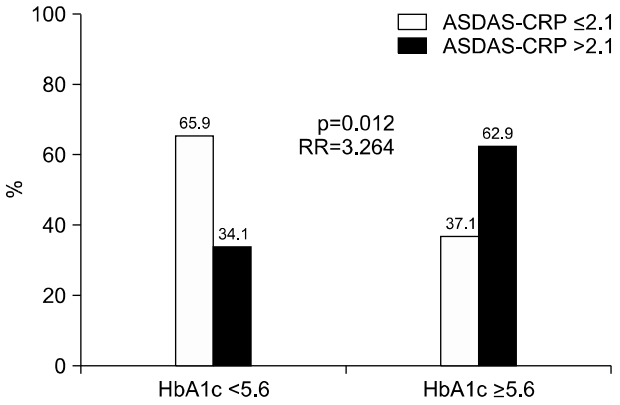

Figure 1. Optimal cut-off values of HbA1c to reflect active ankylosing spondylitis. Active ankylosing spondylitis in patients having HbA1c ≥5.6 was identified more often than in those having HbA1c <5.6 (62.9% vs. 34.1%, p=0.012). Patients having HbA1c more than 5.6 showed significantly enhanced risk of active AS than those having not (RR=3.264). ASDAS: ankylosing spondylitis disease activity score, CRP: C-reactive protein, RR: relative risk, HbA1c: hemoglobin A1c, AS: ankylosing spondylitis.

variate analysis, HbA1c did show a significant difference between active and inactive AS groups based on ASDAS-CRP of 2.1 on univariate analysis (p=0.020). We assumed that this result might result from the relatively low median and mean of ASDAS-CRP as 1.8 and 2.0, which are below the cut-off of 2.1. With this reason, we set the optimal cut-off values of HbA1c to reflect active AS by calculating the area under the receiver operator characteristic curve (AUROC) and selection to maximize the sum of sensitivity (0.611) and specificity (0.675). In addition, the relative risk (RR) of the cut-off value of HbA1c for increased disease activity of AS was analysed using contingency tables and the chi-square test. And we found that 5.6 of HbA1c (AUROC=0.669, 95% CI=0.547, 0.791, p=0.011) was the optimal cut-off value good enough to reflect active AS. When we divided 76 patients with AS into two groups based on the calculated optimal cut-off value of HbA1c, active AS in patients having HbA1c more than 5.6 was identified more often than in those having HbA1c below 5.6 (62.9% vs. 34.1%, p=0.012). Moreover, patients having HbA1c more than 5.6 showed significantly enhanced risk of active AS than those having not (RR=3.264, 95% CI=1.273, 8.369) (Figure 1). If we are able to enrol the larger number of AS patients, we could validate the statistical power of the optimal cut-off value of HbA1c to easily and conveniently categorise active AS or inactive AS in non-diabetic patients.

Previous studies have reported that sulfasalazine and methotrexate treatments can affect HbA1c levels [28,29], so we did univariate regression analysis between these medicines use and HbA1c, but we cannot find statistical significance (data now shown).

The strength of this study is that we first demonstrated that HbA1c was significantly correlated with ASDAS-CRP, and HbA1c could be a useful marker to reflect ASDAS-CRP in AS patients without medical conditions affecting glycated protein levels. Furthermore, we could set the optimal cut-off value of HbA1c at 5.6, and we elucidated that patients having HbA1c more than 5.6 could have enhanced risk of active AS 3.3 times as high as those having not.

We also had several issues: first, our study was a cross-sectional study; second, we did not measure the parameters more directly related to HbA1c level, such as insulin resistance or intramural thickness; third, we could not perform sub-group analysis according to anti-hypertension and anti-dyslipidaemia agents, which can worsen or improve insulin resistance or beta-cell functions [30,31]. If future studies can serially measure not only HbA1c, but also the parameters directly related to HbA1c level, they could provide a dynamic correlation between HbA1c and disease activity of AS. In conclusion, we herein showed that HbA1c was significantly correlated with ASDAS-CRP, and HbA1c could be a useful marker to reflect ASDAS-CRP in AS patients without medical conditions affecting glycated protein levels. Furthermore, we elucidated that patients having HbA1c more than 5.6 could have enhanced risk of active AS 3.3 times as high as those having not.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.2018.25.2.131.

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Supplementary Table 1. Correlation among variables related to glucose metabolism and disease activity of ankylosing spondylitis (n = 76)

	BMI	HbA1c	GA	Fasting glucose	ASDAS-ESR	ASDAS-CRP	BASDAI	BAS-G
BMI	1							
HbA1c	0.227*	1						
GA	−0.268*	0.400*	1					
Fasting glucose	0.331*	0.405*	0.186	1				
ASDAS-ESR	0.013	0.220	0.105	0.011	1			
ASDAS-CRP	0.032	0.315*	0.135	0.037	0.792*	1		
BASDAI	0.019	0.226*	0.192	0.010	0.719*	0.774*	1	
BAS-G	0.039	0.401*	0.221	0.166	0.568*	0.617*	0.655*	1
BASFI	−0.118	0.124	0.111	0.013	0.376*	0.322*	0.211	0.279*

BMI: body mass index, HbA1c: haemoglobin A1c, GA: glycated albumin, ASDAS: ankylosing spondylitis disease activity score, BASDAI: Bath ankylosing spondylitis disease activity index, BAS-G: Bath ankylosing spondylitis patient global score, BASFI: Bath ankylosing spondylitis disease activity functional index. *$p < 0.05$.