The association of Indoxyl sulfate and p-cresyl sulfate with atherosclerotic factor in patients on long-term hemodialysis

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Abstract

Background: Advanced glycation end products (AGEs), a pro-inflammatory and pro-oxidative compounds, play a critical role in endothelial dysfunction and atherosclerosis. Protein-bound uremic toxins – indoxyl sulfate (IS) and p-cresyl sulfate (PCS) have also been reported to inhibit endothelial function. Our objective was to explore the association of IS and PCS with AGEs in a hemodialysis-based cohort.

Methods: This study recruited 129 stable HD patients in a single medical center. Serum levels of total and free IS, PCS and AGEs were measured concurrently. General laboratory results and patient background were also investigated.

Results: The serum levels of AGEs was associated with total IS (r=2.7, p<0.01) not total PCS (r=0.01, NS), free IS (r=0.11, NS) and free PCS (r=0.04, NS) by Pearson's analysis. Multiple linear regression analysis showed total IS was significantly related to AGEs (β=0.296, p<0.01), free IS (β=0.502, p<0.01) and creatinine (β=0.294, p<0.01). Serum AGEs levels correlated significantly and positively with DM status (β=0.250, p=0.01) and total IS (β=0.341, p<0.01) concentrations by another multivariate model. Moreover, patients with DM had higher serum AGEs levels than those without DM (p<0.01).

Conclusion: These findings suggest that the serum levels of total IS were associated with AGEs levels and may participate the process of artherosclerosis.

Results

Table 1. Baseline characteristics of the patients.

	Patient demographics HD patients (n=129)
Median age (y)	65.61 ± 9.12
Men	66 (51.2%)
Women	63 (48.8%)
Time of HD (m)	42.27 ± 21.47
Diabetes	55 (42.6%)
PKD	6 (4.65%)
SLE	2 (1.55%)
cGN	43 (51.2%)
HTN	83 (64.3%)
SBP (mmHg)	146.48 ± 16.08
DBP (mmHg)	86.47 ± 8.27
nPCR (g/kg/day)	1.20 ± 0.11
Kt/V	1.56 ± 0.24
rK/V	0.06 ± 0.08
CO2 (mmol/L)	23.18 ± 1.65
Hb (g/dL)	10.64 ± 1.04
Creatinine (mg/dl)	10.95 ± 2.14
Hct (%)	30.36 ± 3.48
Albumin (g/dL)	4.15 ± 0.27
Calcium (mg/dL)	8.54 ± 0.51
Phosphate (mg/dL)	5.32 ± 1.11
I-PTH (pg/mL)	335.08 ± 187.97
Alk-P (IU/L)	103.01 ± 34.64
hs CRP (mg/dL)	0.72 ± 0.69
Free IS (mg/L)	1.5 ± 0.8
Total IS (mg/L)	38.15 ± 13.08
Free PCS (mg/L)	1.7 ± 0.7
Total PCS (mg/L)	26.03 ± 12.01
AGEs (AU/mL)	12.6 ± 6.2

Table 2. Correlations between serum indoxyl sulfate and p-cresyl sulfate levels and baseline clinical and biochemical characteristics.

Variables	Total PCS r	Total PCS p	Free PCS r	Free PCS p	Total IS r	Total IS p	Free IS r	Free IS p
Age (yrs)	0.16	NS	0.14	NS	-0.07	NS	0.07	NS
Sex	0.04	NS	0.09	NS	0.14	NS	0.08	NS
DM	0.05	NS	0.18	NS	-0.09	NS	0.03	NS
Dialysis time(m)	0.11	NS	0.08	NS	0.21	NS	0.15	NS
Kt/V	-0.02	NS	-0.03	NS	-0.04	NS	0.03	NS
nPCR (g/kg/day)	0.06	NS	-0.08	NS	0.18	NS	-0.05	NS
Albumin (g/dL)	-0.03	NS	-0.25	<0.05	0.21	<0.05	-1.34	NS
Hemoglobin (g/dL)	-0.02	NS	0.06	NS	-0.14	NS	0.06	NS
BUN (mg/dL)	-0.09	NS	-0.12	NS	-0.13	NS	0.03	NS
Creatinine (mg/dL)	-0.14	NS	-0.15	NS	0.29	<0.01	0.07	NS
Uric acid (mg/dL)	0.01	NS	-0.06	NS	0.05	NS	-0.04	NS
Na (mg/dL)	0.05	NS	-0.18	NS	0.17	NS	0.14	NS
K (mg/dL)	0.11	NS	0.03	NS	0.20	<0.01	0.13	NS
Calcium (mg/dL)	0.04	NS	-0.06	NS	0.01	NS	0.16	NS
Phosphate (mg/dL)	-0.01	NS	0.06	NS	0.03	NS	-0.05	NS
Alk-p (IU/L)	-0.05	NS	0.16	NS	0.14	NS	0.22	<0.05
I-PTH (pg/mL)	0.03	NS	0.12	NS	0.09	NS	-0.11	NS
hsCRP (mg/dL)	0.05	NS	0.14	NS	-0.06	NS	0.25	<0.05
AGEs (AU/mL)	0.01	NS	0.04	NS	0.27	<0.01	0.11	NS

Table 3. Stepwise multiple linear regression analysis for total indoxyl sulfate as a dependent variable.

Variables	Unstandardized coefficients B	Unstandardized coefficients Std. Error	Standardized coefficients Std. Error	p value
DM	3.672	1.545	0.250	0.01
Total IS	0.200	0.058	0.341	<0.01

This model included gender, age, DM, duration on hemodialysis, Kt/V, Cr, albumin, P, i-PTH , AGEs, free IS, total PCS.

Table 4. Stepwise multiple linear regression analysis for AGEs as a dependent variable.

Variables	Unstandardized coefficients B	Unstandardized coefficients Std.Error	Standardized coefficients Std. Error	p value
AGES	0..482	0.138	0.296	<0.01
Free IS	5.699	0.961	0.502	<0.01
Creatinine	1.545	0.443	0.294	<0.01

This model included gender, age, DM, duration on hemodialysis, Kt/V, Cr, hsCRP, albumin, Ca, P, i-PTH, total IS, free IS, total PCS, free PCS.
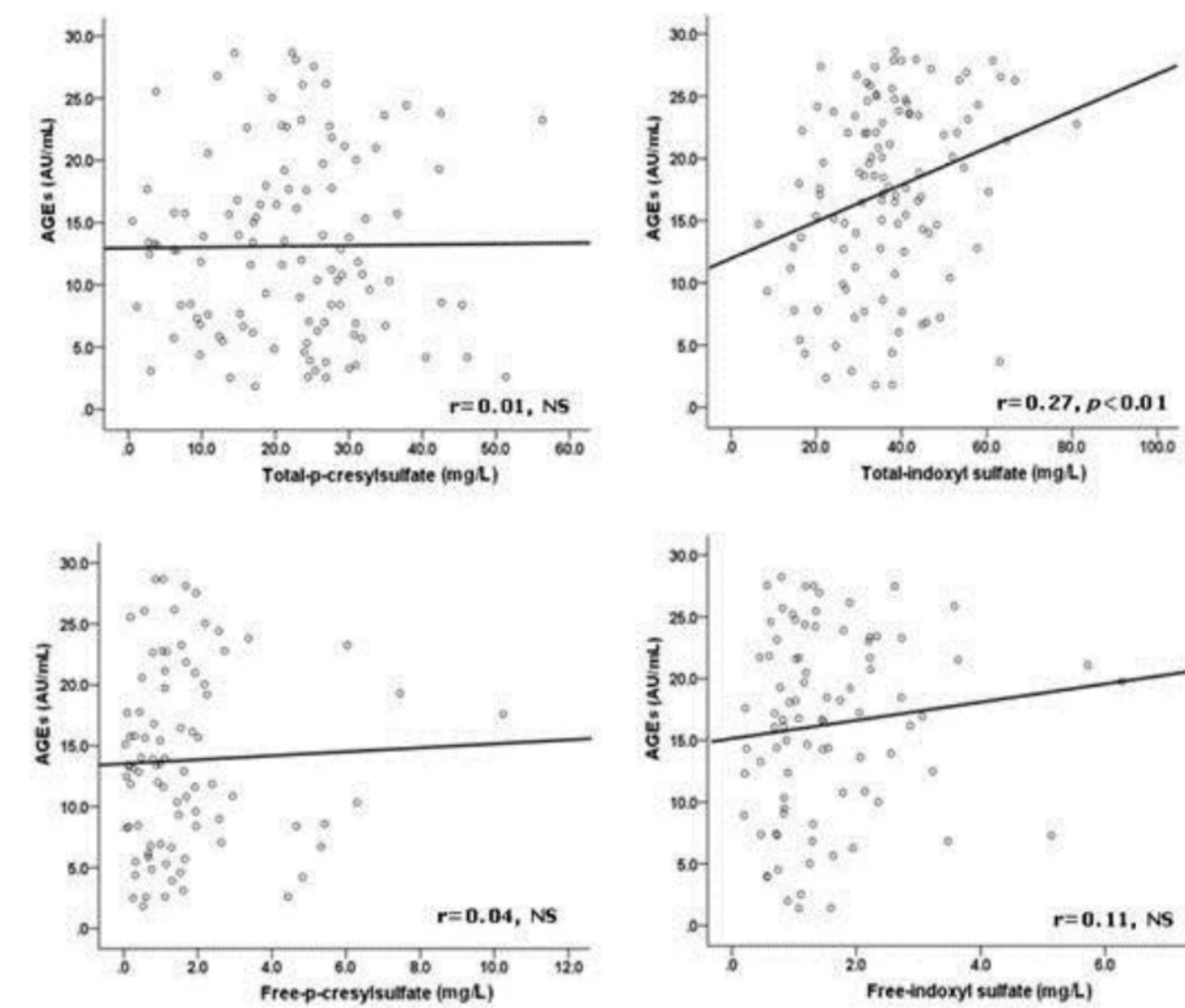

Figure 1. Correlations between AGEs and (A) total PCS, (B) total IS (C) free PCS and (D) free IS in HD patients.
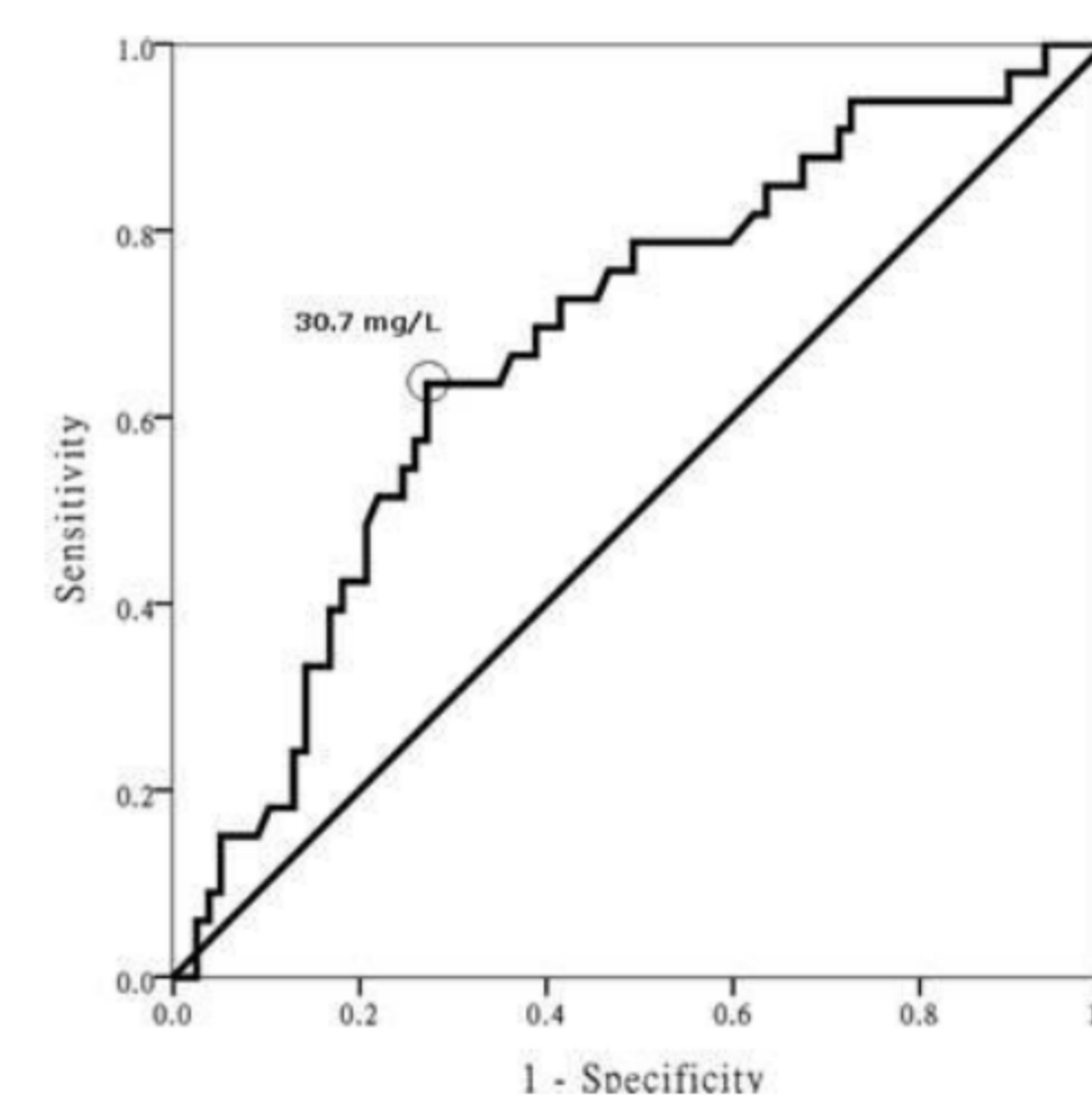

Figure 2. Receiver-operating characteristic (ROC) curve of weight for predicting the serum indoxyl sulfate levels. The optimum cut-off point (open circle) was defined as the closest point on the ROC curve to the point (X, Y)=(0, 1), where X=1 – specificity and Y = sensitivity.

Table 5. The comparisons of independent variables in HD patients stratified by indoxyl sulfate levels.

| Variables	High Indoxyl sulfate >30.7 mg/L	Low Indoxyl sulfate ≦30.7 mg/L	p-value
Median age (y)	58.31±11.7	62.15±11.9	NS
Time of HD (m)	43.13±22.43	41.98±21.54	NS
Diabetes	45.4%	57.6%	NS
nPCR (g/kg/day)	1.16±0.25	1.03±0.28	0.040
Kt/V	1.42±0.27	1.41±0.24	NS
CO2 (mmol/L)	22.37±1.98	23.72±2.01	NS
Hb (g/dL)	10.41±1.33	10.88±1.54	NS
Creatinine (mg/dl)	10.98±2.14	9.33±2.38	<0.01
Albumin (g/dL)	4.17±0.31	3.97±0.32	0.01
Calcium (mg/dL)	9.26±0.73	9.27±0.80	NS
Phosphate (mg/dL)	5.51±1.53	5.19±1.38	NS
I-PTH (pg/mL)	381.92±298.47	264.33±220.61	0.03
Alk-P (IU/L)	104.83±52.05	101.42±37.77	NS
hs CRP (mg/dL)	1.51±	0.82±	NS
Free PCS (mg/L)	1.56±1.51	1.86±2.23	NS
Total PCS (mg/L)	22.68±11.81	20.42±10.53	NS
AGEs (AU/ml)	16.3±6.9	11.7±7.0	<0.01
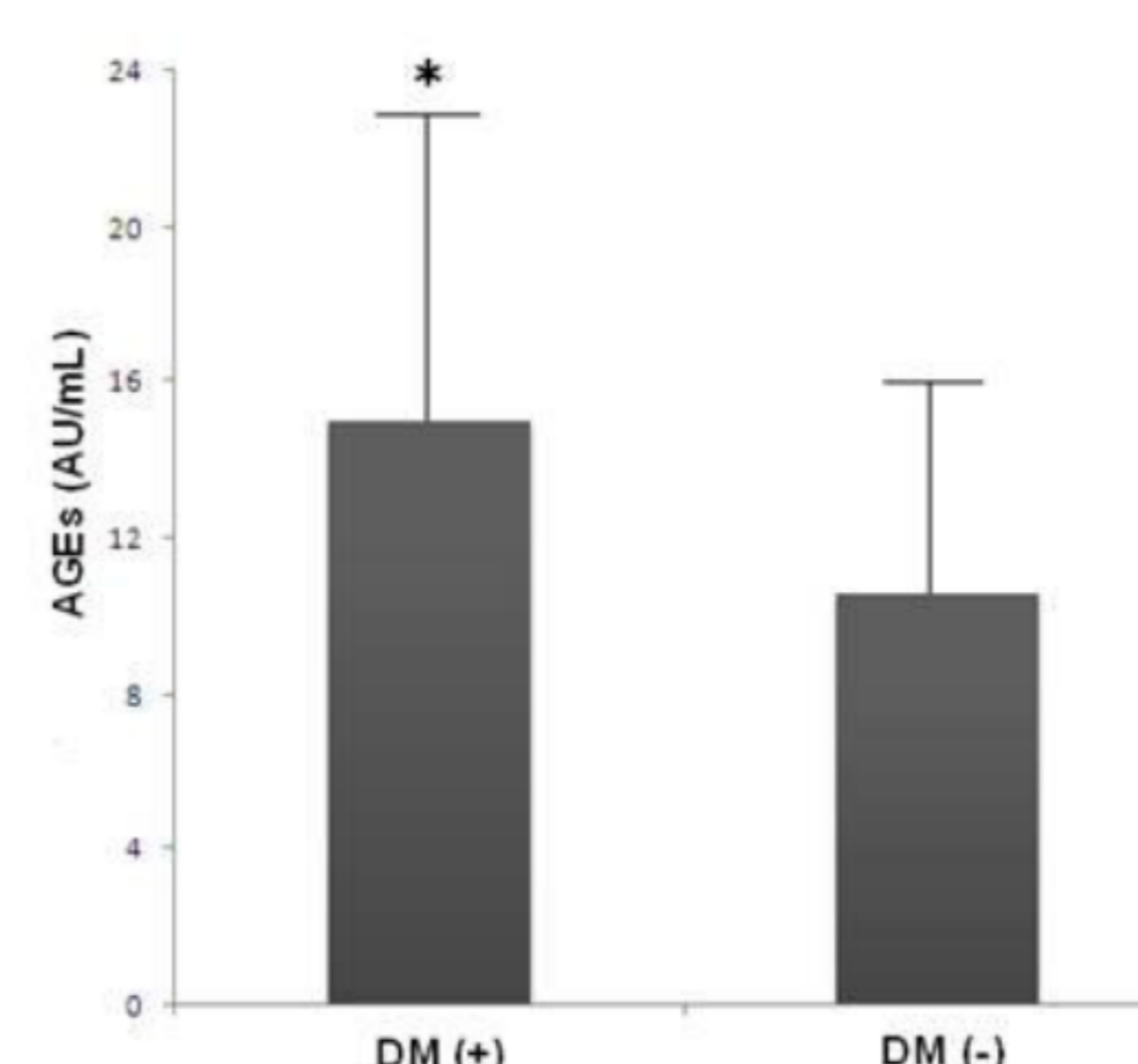
Figure 3. The comparison of serum AGEs levels in HD patient with and without DM, * p<0.01.