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ORIGINAL RESEARCH

Association Between Systemic Immune-Inflammation Index and Diabetic Depression

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Background: Depression is highly prevalent in patients with diabetes mellitus (DM). Diabetic depression has been shown to be associated with low-grade systemic inflammation. In recent years, the systemic immune-inflammation (SII) index has been developed as an integrated and novel inflammatory indicator. The aims of this study were to investigate the relationship between diabetic depression and SII levels, adjusting for a wide range of potential confounding factors, to examine the potential of SII in predicting diabetic depression.

Methods: The present cross-sectional study was conducted among adults with DM in the National Health and Nutrition Examination Survey between 2009 and 2016, the SII level was calculated as the platelet counts × neutrophil counts/lymphocyte counts. Patient Health Questionnaire-9 was used to measure depression in patients with DM. Multivariable logistic regression and propensity score-matched analysis were used to analyze the association between SII levels and depression.

Results: A total of 2566 patients with DM were included in the study, of which 370 (13.3%) were diagnosed with depression. Multivariable logistic regression showed that high SII level was an independent risk factor for diabetic depression (OR = 1.347, 95% CI: 1.031–1.760, P = 0.02882) after adjusting for covariates. The relationship between SII and diabetic depression was further verified by propensity score-matched analysis.

Conclusion: Our data suggest that SII is a risk factor for depression in patients with DM. The SII may be an easily accessible and cost-effective strategy for identifying depression in patients with DM. More studies are warranted to further analyze the role of SII in depression in diabetic patients.

Keywords: systemic immune-inflammation index, depressive symptoms, diabetes mellitus, NHANES

Introduction

Diabetes mellitus (DM) is one of the most prevalent chronic diseases in recent decades.[1] In patients with DM, 64% experience psychological distress and 8% to 35% are diagnosed with depression.[2–5] Patients with DM and depression tend to be less adherent to their therapy and have a higher rate of death.[6] The complications associated with diabetes can also increase the risk of depression. Approximately 51% of depression cases are not correctly diagnosed in patients with DM, and only 31% received adequate antidepressants.[7] Therefore, it is both urgent and necessary to identify depression in patients with DM.

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Preclinical and clinical studies have shown a causal link between sterile low-grade inflammation and depression in patients with DM.[8–12] Study showed that a high-fat diet leads to an increase in inflammatory cytokine levels and to anxiety and depressive behaviors.[13,14] Antidepressant administration decreased the inflammatory cytokine levels and reversed the behavioral deficits caused by a high-fat diet.[15] Inflammatory biomarkers could potentially be used to predict depression in diabetic patients. Abnormal increases in inflammatory blood cell parameters including neutrophil count, neutrophil-to-lymphocyte ratio,[16,17] monocyte-to-lymphocyte ratio,[18] and platelet-to-lymphocyte ratio[19,20] serve as simple markers of inflammation and their ability to predict depression has been assessed. But these biomarkers involve only two types of immune-inflammatory cells and might not accurately reflect the inflammation status.

The systemic immune-inflammation index (SII) is an integrated and novel inflammatory biomarker[21,22] based on neutrophil, lymphocyte, and platelet counts. The SII index was initially used to assess the prognosis of patients with solid cancers[22] and coronary heart disease (CHD)[23] and is now considered to accurately reflect inflammation status.[24] However, the role of SII in depression in patients with DM remains unclear. We hypothesized that patients with DM and higher levels of inflammation, as measured by SII, are at a higher risk of developing depression. Therefore, we performed a cross-sectional study to assess the relationship between diabetic depression and SII levels to determine the value of SII in predicting diabetic depression.

Methods

Data and Sample Sources

The study was a two-year cross-sectional, stratified, multistage probability cluster survey. Data were obtained from the National Health and Nutrition Examination Survey (NHANES),[25] which is designed to collect a wide variety of information on the potential risk factors and nutrition of the non-institutionalized, civilian, US population. The protocols for the conduct of NHANES were approved by the National Center for Health Statistics institutional review board (NCHS IRB/ERB), and informed consent was obtained from all participants (NCHS IRB/ERB protocols #2011–17). The Ethics Review Board for the National Center for Health Statistic (NCHS ERB) approved the NHANES (NCHS ERB protocols #2011–17), and all participants gave written informed consent. Following an in-home interview, NHANES participants receive a health examination at mobile examination centers. The medical and physiological status of participants is assessed, and laboratory tests conducted. Four cycles of the NHANES survey were selected to assess the association between SII and diabetic depression. The exclusion criteria were: (a) patients with missing SII data and incomplete Patient Health Questionnaire-9 (PHQ-9),[26] and (b) corticosteroid, and nonsteroidal anti-inflammatory drug use.

Assessment of Depression Symptoms

In NHANES, depression was assessed using the PHQ-9.[26] The PHQ-9 form was completed during the face-to-face mobile exam center interview and was designed to evaluate any depression symptoms in the preceding 2 weeks. Each item on the form was scored on a scale of 0 to 3, and total scores ranged from 0 to 27. In this study, PHQ-9 score $\geq$ 10 was considered to indicate depression, with a specificity and sensitivity of 88%.[27,28]

Study Variables

Lymphocyte, neutrophil, and platelet counts were evaluated using automated hematology analyzing devices and were expressed as $\times 10^3$ cells/μL. The SII level was measured as platelet count x neutrophil count/lymphocyte count.[21] Details of methods about blood are described in the Supporting Methods section. Demographic characteristics included age, sex, race, marital status, education level, body mass index (BMI), smoking status, and ratio of family income to poverty (PIR); DM-related characteristics glycated hemoglobin A1c (HbA1c), diabetes duration, diabetic retinopathy (DR) and insulin use; health factors included stroke, heart failure (HF), and CHD.

Statistical Analyses

Differences in baseline characteristics in the depressive and the non-depressive-symptoms groups were compared using an independent sample *t*-test for continuous variables and $\chi 2$ tests for categoric variables. For the current study, the optimal cutoff value for the SII level was determined using receiver operating characteristics curve analysis. We performed multivariate logistic regression analysis to examine the association between SII and diabetic depression, with 95% confidence intervals (CI) and odds ratio (OR) calculated. In model 1, any confounding factors were not adjusted for, and age, sex, race, education, marital status, body mass index, HbA1c, insulin use, poverty income ratio, smoking status, diabetes duration, chronic conditions

including stroke (yes/no), CHD (yes/no), and HF (yes/no), were adjusted for in model 2. To avoid potential bias, and because of differences in baseline characteristics, the propensity score matching (PSM) was determined.[29] The study was used to ensure all reported depression selection factors were included as covariates in the model to further reduce potential confounding. Final covariates were age, sex, race, education, marital status, body mass index, HbA1c, insulin use, poverty income ratio, smoking status, diabetes duration, diabetic retinopathy, chronic conditions including stroke (yes/no), CHD (yes/no), and HF (yes/no). PSM was performed at a ratio of 1:1 using a caliper width of 0.01 of the SD of the logit of the propensity score. After PSM, model 3 was analyzed. Subgroup analysis was performed to explore if the association differed for subgroups classified using different parameters including age, sex, BMI, HbA1c, and insulin use. We conducted linear regression analyses to examine the association of SII (independent variable) and high sensitive c-reactive protein (hs-CRP), neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio (dependent variable) to examine whether SII level were associated with inflammation levels.

All analyses were performed using R (version 4.00) "MatchIt" package for PSM. $P < 0.05$ (two-sided) indicated significant difference.

Results

Subject Characteristics

We identified 2566 patients with DM who met our inclusion criteria. The eligible participants included 1252 women and 1314 men with a mean age of 61.4 ± 13.1 years, and a mean SII of 557.4. The number of patients diagnosed with diabetic depression was 370 (14.4%). Baseline characteristics are shown in Table 1. Depression in patients was associated with higher levels of BMI, heart failure, stroke, and SII. They were also less likely to have been married, and more likely to be in the lower age group and have a lower PIR rate ($p < 0.05$). Education, diabetic retinopathy, and CHD did not differ between patients with and without depression.

SII is an Independent Risk Factor for Diabetic Depression

We constructed various models to assess the independent effects of SII on diabetic depression, after adjusting for other potential confounding factors. In univariate analysis, age, sex, race, education, BMI, PIR, smoking status, marital status, and chronic conditions were associated with a higher risk of depression ($p < 0.05$, Supplementary Materials Table S1). High SII levels were a risk factor for diabetic depression in univariate analysis (OR = 1.687, 95% CI: 1.351–2.107, $P < 0.00001$, Table 2). After adjusting for age, sex, race, education, marital status, body mass index, HbA1c, insulin use, poverty income ratio, smoking status, diabetes duration, chronic conditions including stroke (yes/no), CHD (yes/no), and HF (yes/no), high SII levels were an independent risk factor for diabetic depression (OR = 1.347, 95% CI: 1.031–1.760, P =0.02882). We excluded participants who had a diagnosis of coronary heart disease, stroke, and heart failure, a significant relationship between SII and depression still present (Supplementary Materials Table S2).

PSM Analysis

PSM analysis was conducted to assess the relationship between SII and diabetic depression. The baseline characteristics of patients in different SII groups did not significantly differ (Table 3). Logistic regression analysis revealed that high SII levels were independently related to diabetic depression (OR = 1.452, 95% CI: 1.104–1.908, $p = 0.00755$).

Subgroup Analysis

Subgroup analysis results are shown in Table 4. In patients with diabetic depression, there were no differences in SII levels in most pre-specified subgroups, with the exception of sex. High SII levels were independently related to depression in male patients (OR = 1.686, 95% CI: 1.162–-2.447, $p = 0.0059$), but not in female patients.

Associations Between SII and Inflammatory Markers

Correlations between SII and inflammatory markers are summarized in Table 5. The SII levels were significantly correlated with the inflammatory markers (hs-CRP, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio) in the diabetes mellitus ($P<0.001$), and these correlations were stronger in depressive symptoms (hs-CRP, r = 0.6073, $P <0.001$)

Discussion

To the best of our knowledge, this is the first study that demonstrates the close association between SII and depression in people with DM. Our results show that patients with DM suffering from depression had significantly higher SII levels than did those without depression.

Table 1 Characteristics of Participants in the NHANES (2009–2016) by Depression Status[a]

	Diabetes Mellitus (n=2196)	Diabetic Depression[b] (n=370)	*p*
Age (years)	61.8 ± 13.1	59.0 ± 12.8	<0.001
Male	1191 (54.2)	123 (33.2)	<0.001
Race (%)			<0.001
Mexican American	387 (18.1)	75 (20.7)	
Other Hispanic	262 (12.2)	72 (19.8)	
Non-Hispanic White	646 (30.1)	110 (30.3)	
Non-Hispanic Black	609 (28.4)	92 (25.3)	
Other	240 (11.2)	14 (3.9)	
PIR	2.3 ± 1.5	1.4 ± 1.1	<0.001
Education (%)			0.135
Primary school	1003 (45.8)	188 (50.8)	
High school	599 (27.4)	85 (23.0)	
Above	586 (26.8)	97 (26.2)	
Marital status			<0.001
Married/living with partner	1322 (60.5)	167 (45.1)	
Widowed/ divorced	669 (30.6)	155 (41.9)	
Never married	195 (8.9)	48 (13.0)	
BMI (kg/m^2)	32.2 ± 7.2	35.2 ± 9.2	<0.001
Smoking (%)			<0.001
Never smoker	1124 (51.5)	161 (43.5)	
Former smoker	748 (34.2)	124 (33.5)	
Current smoker	312 (14.3)	85 (23.0)	
SII	546.2 ± 362.3	623.1 ± 393.6	<0.001
DM-related characteristics			
HbA1c (%)	7.4 ± 1.8	7.6 ± 2.2	0.079
Diabetes duration (years)	10.9 ± 9.0	10.6 ± 8.8	0.783
Insulin use (%)			0.210
Yes	567 (25.9)	107 (29.0)	
No	1623 (74.1)	262 (71.0)	
Diabetic retinopathy (%)			0.206
Yes	491 (22.5)	93 (25.5)	
No	1694 (77.5)	272 (74.5)	
Chronic conditions heart failure (%)			<0.001
Yes	191 (8.8)	60 (16.3)	
No	1986 (91.2)	308 (83.7)	
Coronary heart disease (%)			0.087
Yes	226 (10.4)	49 (13.4)	
No	1945 (89.6)	316 (86.6)	
Stroke (%)			0.007
Yes	178 (8.1)	46 (12.5)	
No	2009 (91.9)	323 (87.5)	

Notes: [a]Data are weighted estimates, and values are presented as means ± standard deviation or means (percentage). [b]Depressive symptom measured using Patient Health Questionnaire (PHQ-9) and Depression (PHQ-9≥10).
Abbreviations: NHANES, National Health and Nutrition Examination Survey; PIR, poverty income ratio; BMI, body mass index; SII, systemic immune-inflammation index; DM, diabetes mellitus.

Table 2 Association Between SII and Diabetic Depression

SII	OR	95% CI	P
Model 1[a]			
<557.5	Reference		
≥557.5	1.687	1.351–2.107	<0.00001
Model 2[b]			
<557.5	Reference		
≥557.5	1.347	1.031–1.760	0.02882
Model 3[c]			
<557.5	Reference		
≥557.5	1.452	1.104–1.908	0.00755

Notes: [a]Model 1 did not adjust for any confounding factors. [b]Model 2 adjusted for age, sex, race, education, marital status, body mass index, HbA1c, insulin use, poverty income ratio, smoking status, diabetes duration, chronic conditions including stroke (yes/no), CHD (yes/no), and HF (yes/no). [c]Model 3 after propensity score.
Abbreviations: SII, systemic immune-inflammation index; OR, odds ratio; CI, confidence interval.

Additionally, high SII levels were an independent risk factor for diabetic depression.

As a major mental illness, depression is an important chronic comorbidity of DM.[30] Multiple meta-analyses show that DM is a risk factor for depression, and a bi-directional relationship has been shown between the two.[6,31–33] Studies

Table 3 Characteristics of Patients Before and After PSM[a]

	Before Propensity Score		After Propensity Score[c]	
	<557.5 (n=1395)	**≥557.5 (n=1171)**	**< 557.5 (n=793)**	**≥557.5 (n=793)**
Age (years)	64.1 ± 12.1	58.1± 13.5*	61.11 ± 12.20	60.68 ± 12.33
Male, n (%)	853 (61.1)	461 (39.4) *	404 (50.9)	387 (48.8)
Race, n (%)				
Mexican American	253 (18.5)	209 (18.3)	142 (17.9)	140 (17.7)
Other Hispanic	170 (12.4)	164 (14.4)	95 (12)	122 (15.4)
Non-Hispanic White	435 (31.8)	321 (28.2)	251 (31.7)	241 (30.4)
Non-Hispanic Black	388 (28.0)	318 (27.9)	237 (29.9)	204 (25.7)
Other	126 (9.2)	128 (11.2)	68 (8.6)	86 (10.8)
PIR	2.2 ± 1.5	2.2 ± 1.5	2.2 ± 1.5	2.2 ± 1.5
Education, n (%)				
Primary school	666 (47.9)	525 (45.0)	258 (32.5)	244 (30.8)
High school	379 (27.2)	305 (26.1)	197 (24.8)	231 (29.1)
Above	346 (24.9)	337 (28.9)	338 (42.6)	318 (40.1)
Marital status, n (%)		*		
Married/partner	837 (60.2)	652 (56.0)	463 (58.4)	461 (58.1)
Widowed/divorced	445 (32.0)	379 (32.5)	255 (32.2)	254 (32)
Never married	109 (7.8)	337 (28.9)	75 (9.5)	78 (9.8)
BMI (kg/m^2)	31.9 ± 7.0	33.4 ± 8.0*	32.57 ± 7.49	33.08 ± 8.13
Smoking (%)				
Never smoker	700 (50.3)	587 (50.3)	402 (50.7)	387 (48.8)
Former smoker	493 (35.4)	380 (32.6)	266 (33.5)	285 (35.9)
Current smoker	198 (14.2)	200 (17.1)	125 (15.8)	121 (15.3)
DM-related characteristics				
Fasting Glucose (mg/dL)	157.7 ± 63.9	158.9± 65.6	160.4 ± 67.0	154.9 ± 61.3
HbA1c (%)	7.4 ± 1.8	7.6 ± 1.9*	7.5 ± 2.0	7.5 ± 1.8
Diabetes duration (years)	11.1 ± 9.1	10.5 ± 8.8	11.1 ± 9.2	10.9 ± 9.0
Insulin use, n (%)				
Yes	322 (25.2)	352 (27.5)	206 (26)	182 (23)
No	956 (74.8)	929 (72.5)	585 (74)	609 (77)
DR, n (%)				
Yes	318 (22.9)	266 (22.9)	175 (22.1)	175 (22.1)
No	1069(77.1)	897 (77.1)	618 (77.9)	618 (77.9)
HF, n (%)		*		
Yes	168 (12.2)	83 (7.1)	62 (7.8)	62 (7.8)
No	1213 (87.8)	1081 (92.9)	731 (92.2)	731 (92.2)
CHD, n (%)		*		
Yes	191 (13.9)	84 (7.2)	67 (8.4)	66 (8.3)
No	1184 (86.1)	1077 (92.8)	726 (91.6)	727 (91.7)
Stroke, n (%)				
Yes	127 (9.1)	97 (8.3)	71 (9)	70 (8.8)
No	1264 (90.9)	1068 (91.7)	722 (91)	723 (91.2)

(*Continued*)

Table 3 (Continued).

	Before Propensity Score		After Propensity Score[c]	
	<557.5 (n=1395)	≥557.5 (n=1171)	< 557.5 (n=793)	≥557.5 (n=793)
Depression[b], n (%)		*		*
Yes	160 (11.5)	210 (17.9)	105 (13.3)	144 (18.2)
No	1235 (88.5)	961 (82.1)	687 (86.7)	649 (81.8)
PHQ-9 scores	3.9 ± 4.9	4.8 ± 5.3*	4.2 ± 5.1	4.8 ± 5.4*

Notes: [a]Data are presented as means ± standard deviation or means (percentage). [b]Depressive symptom measured using Patient Health Questionnaire (PHQ-9) and Depression (PHQ-9≥10). [c]1:1 matching for age, sex, race, education, marital status, body mass index, HbA1c, insulin use, poverty income ratio, smoking status, diabetes duration, diabetic retinopathy, chronic conditions including stroke (yes/no), CHD (yes/no), and HF (yes/no). *$p<0.05$.
Abbreviations: PSM, propensity score matching; SII, systemic immune-inflammation index; BMI, body mass index; DM, diabetes mellitus; CHD, coronary heart disease; HF, heart failure; DR, diabetic retinopathy; PIR, ratio of family income to poverty.

show that 20% to 40% of individuals with diabetes experienced symptoms of depression.[33] Depression is associated with poor health behaviors, including smoking, physical inactivity, and caloric intake, that increase the risk of diabetes.[34] Depression is associated with macrovascular complications,[35] all of which cause mortality in patients with diabetes.[36] It is important to identify biomarkers for early detection of depression in patients with diabetes. A potential link between chronic inflammatory states and depression has also been proposed.[37]

SII was determined based on the counts of three types of circulating immune cells: neutrophils, lymphocytes, and platelets. The SII level reflects the inflammatory state and could serve as a readily detectable biomarker for systemic inflammatory activity.[38] Our results show that patients with diabetes suffering from depression had significantly higher SII levels than did those without depression and that high SII levels are an independent risk factor for diabetic depression. After matching the possible confounding factors, we found that SII, the neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio were associated with depression, but that SII had the highest risk. The SII level provides more clinical information than do NLR and PLR. Patients with high SII levels often have thrombocytosis, neutrophilia, or lymphopenia.[39] Lymphocytes and neutrophils mediate adaptive and innate immunity. Neutrophils, which constitute the largest proportion of white blood cells, are important for initiating and modulating immune processes[40] and secrete neutrophil elastase to mediate chronic inflammation.[41] Patients with increased neutrophil activity release reactive oxygen species, which may be involved in the development of depression. Lymphocytes are an important component of leukocytes, mediate adaptive immunity, and function in innate immunity. Lymphocytes are specific inflammatory mediators with regulatory or protective effects.

Table 4 Subgroup Analysis of the Associations Between SII and Diabetic Depression

	N	OR (95% CI)	P
Age (years)			
<60	968	1.683(1.190–2.380)	0.0032
≥60	1598	1.555 (1.155, 2.093)	0.0036
Sex			
Male	1314	1.686 (1.162–2.447)	0.0059
Female	1252	1.077 (0.808–1.434)	0.6133
BMI[a]			
Normal weight	307	1.390 (0.653–2.958)	0.39311
Overweight	712	2.164 (1.289–3.632)	0.00349
Obese	1478	1.551 (1.185–2.030)	0.00138
HbA1c (%)			
<7.0	1255	1.871 (1.363–2.567)	0.0001
≥7.0	1287	1.505 (1.097–2.066)	0.0113
Insulin use			
No	1885	1.375 (1.057–1.788)	0.0176
Yes	674	1.822 (1.187–2.798)	0.0061

Note: [a]BMI was categorized as normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30 kg/m^2).
Abbreviations: SII, systemic immune-inflammation index; OR, odds ratio; CI, confidence interval; BMI, body mass index.

Platelets can be considered an aspecific first line inflammatory marker that can bind to leukocytes and the endothelium, influencing the function of inflammatory elements of these cells. Inflammatory elements including cytokines, epinephrine, serotonin, glutamate, dopamine, and P-selectin can activate platelets.[42] Serotonin, glutamate, and other proinflammatory molecules such as IL-1, CD40L, and P-selectin originate from activated platelets and modulate platelet function in the pathophysiology of depression.[43,44] The dense granules within platelets also contain glutamate[42,45] and platelets are activated in patients with depression. Our

Table 5 Correlations Between SII vs Different Variables in All Subjects and Depressive Symptoms

	All Subjects		Without Depressive Symptoms[a]		With Depressive Symptoms	
	Pearson r[b]	*p*	Pearson r	*p*	Pearson r	*p*
hs-CRP	0.3501	<0.0001	0.2981	<0.0001	0.6073	<0.0001
NLR	0.8403	<0.0001	0.8508	<0.0001	0.7968	<0.0001
PLR	0.7469	<0.0001	0.7515	<0.0001	0.7297	<0.0001

Notes: [a]Depressive symptom measured using Patient Health Questionnaire 9; Without Depressive Symptoms (PHQ-9<10), With Depressive Symptoms (PHQ-9≥10). [b]Linear regression was used for the analysis.

Abbreviations: SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; hs-CRP, high sensitive C-reactive protein.

results show that high SII levels are an independent risk factor for diabetic depression.

A single study that analyzed inflammation and CHD risk in patients with depression found that SII was significantly higher in patients with major depressive disorder than in the control group.[46] However, further analysis was not performed, and the researchers did not adjust for potential confounding factors.

Our study had several strengths. The sample size in this study was large enough to identify a significant association between SII and depression in patients with diabetes. Moreover, the analysis of detailed covariate data allowed us to adjust for potential confounding factors that might influence the association between SII and depression. However, there are some limitations to our study. Firstly, the cross-sectional study design means that causality cannot be established. Prospective studies are needed to establish causality. Secondly, data used in this study were extracted from one blood test only. Serial testing may be more informative than a single test on admission because of the short life span of blood cells. Thirdly, SII is easy to measure in clinical practice but the loss of neutrophils, lymphocytes, and platelet counts is common and may lead to selection bias.

Conclusion

Here, we provide the first evidence that SII levels are associated with an increased risk of depression in patients with diabetes. This should be confirmed in prospective studies.

Data Sharing Statement

Publicly available datasets were analyzed in this study. The authors confirm that these data can be found here: https://www.cdc.gov/nchs/nhanes/.

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Disclosure

The authors report no conflicts of interest for this work.

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