Metabolic and Inflammatory Links to Depression in Youth With Diabetes

Korey K. Hood, phd[1]
Jean M. Lawrence, scd, mph, mssa[2]
Andrea Anderson, ms[3]
Ronny Bell, phd[3]
Dana Dabelea, md, phd[4]

Stephen Daniels, md, phd[5]
Beatriz Rodriguez, md[6]
Lawrence M. Dolan, md[7]
for the SEARCH for Diabetes in Youth Study Group

OBJECTIVE—Youth with diabetes are at increased risk for depression. The objectives of this study were to provide preliminary evidence that this at-risk status for depression is associated with metabolic and inflammatory markers and to inform future, more stringent examinations of the directionality of these associations.

RESEARCH DESIGN AND METHODS—Data from SEARCH for Diabetes in Youth (SEARCH), an observational study of U.S. children diagnosed with diabetes at <20 years of age, were used for these analyses. SEARCH participants were drawn from four geographically defined populations in Ohio, Washington, South Carolina, and Colorado; health plan enrollees in Hawaii and California; and Indian Health Service beneficiaries from four Native American populations. Participants were 2,359 youth with diabetes from the 2001 prevalent and 2002–2004 incident SEARCH cohorts. Depression was measured with the Center for Epidemiologic Studies Depression scale. Eight metabolic and inflammatory markers were measured: adiponectin, leptin, C-reactive protein, serum amyloid A, apolipoprotein B (apoB), lipoprotein A, interleukin-6, and LDL.

RESULTS—Six of eight markers were significantly ($P < 0.006$) associated with depression in youth with diabetes in bivariate analyses. In general, higher levels of depression were associated with indicators of worse metabolic or inflammatory functioning. In regression models stratified by diabetes type and accounting for demographic and clinical characteristics, only higher levels of apoB remained associated with higher levels of depression in youth with type 1 diabetes.

CONCLUSIONS—These data suggest that depression reported by youth with diabetes is partially associated with metabolic abnormalities and systemic inflammation.

Diabetes Care 35:2443–2446, 2012

Depression is a common comorbid condition in individuals with type 1 or type 2 diabetes (1). Depression is linked to poorer diabetes management and control in both children and adults (2,3). Much of this increased risk for depression and associated morbidities is attributed to the lifestyle aspects of disease management and the burden of managing a chronic condition. Although recent reports suggest the possibility of biological links to depression in adults with diabetes, such as lipid abnormalities and systemic inflammation (4), studies have not examined metabolic and inflammatory factors as biological correlates of depression in youth with diabetes. Given the studies implicating immune system activity in both diabetes and depression (5–7) and the absence of data on correlates and directional pathways, this analysis was undertaken to evaluate the potential for a biological link between depression and metabolic and inflammatory markers. We hypothesized that higher levels of depressive symptoms would be associated with metabolic abnormalities and systemic inflammation in youth with diabetes. To test this, we conducted a cross-sectional investigation of these potential associations in the SEARCH for Diabetes in Youth (SEARCH) cohort.

RESEARCH DESIGN AND METHODS—SEARCH is an observational study of youth in the United States with diabetes diagnosed before the age of 20 years. SEARCH participants are drawn from four geographically defined populations in Ohio, Washington, South Carolina, and Colorado; health plan enrollees in Hawaii and California; and Indian Health Service beneficiaries from four Native American populations. SEARCH participants were eligible for inclusion in this analysis if they were part of the 2001 (prevalent) or 2002–2004 (incident) cohorts and completed the study visit.

At the study visit, demographic, diabetes, depression, and laboratory data were collected. Depression was measured with the Center for Epidemiologic Studies Depression (CES-D) scale; a 20-item, questionnaire that is widely used and has been adapted for use with children and adolescents (8). Higher scores indicate more depressive symptoms. Anthropometric measurements (height and weight) were obtained to calculate BMI. A fasting venipuncture was performed in each participant as part of a separate SEARCH study aim to investigate metabolic and inflammatory markers associated with type of diabetes and insulin resistance. As part of this protocol, the following analytes were measured: adiponectin, leptin, C-reactive protein (CRP), serum amyloid A (SAA), apolipoprotein B (apoB), lipoprotein A (LPA), interleukin-6 (IL-6), and LDL. Hemoglobin A_{1c} was also obtained via this fasting venipuncture. The eight markers have been examined as indicators of metabolic

abnormalities and systemic inflammation in adults with depression.

To test the hypothesis that depression was positively associated with metabolic and inflammatory marker levels, CES-D scores were grouped into no or minimal depression (score of 0–15), mild depression (score of 16–23), and moderate or severe depression (≥24). These categories correspond to cutoffs in large, national samples of adolescents (9) that distinguish depressive symptoms in terms of their severity and likelihood of later recurrence. In addition, these categories have been used previously in SEARCH publications (10). Analysis of variance was conducted with the Kruskal-Wallis correction for nonnormal distributions to test marker levels between depression categories (i.e., does the level of apoB vary significantly by depression level?). This was done in the full sample and by diabetes type. $P < 0.006$ was set to indicate statistical significance given multiple bivariate tests (i.e., Bonferroni correction).

Next, to test the relationships of the markers with depression categories while considering demographic and clinical characteristics, regression models in the general linear model framework were run with each marker as a separate outcome, stratified by diabetes type. Six of the markers (CRP, SAA, apoB, leptin, LPA, and IL-6) were log transformed to address nonnormal distributions in marker levels. Demographic and clinical covariates included in each model were participant age at study visit, sex, race or ethnicity, highest parental education, health insurance coverage (no insurance, private insurance, or public insurance), number of caregivers in the home, duration of diabetes, BMI, and hemoglobin A_{1C}. Note that analyses were not conducted for the small sample ($n = 19$) of youth with "other" types of diabetes. All analyses were completed with SAS software (version 9.2).

RESULTS—The mean age of the 2,359 participants included in this analysis was 15.2 ± 3.1 years and the sample was 53% female, 68% non-Hispanic white, and 85% had type 1 diabetes (Table 1). In total, 22% of the participants were found to have mild to moderate or severe depressive symptoms by virtue of exceeding established cutoffs for the CES-D scale. With regard to the eight inflammatory and metabolic markers, the means and SDs are displayed by diabetes type and depression category in Table 2. In the full sample, there were significant differences ($P < 0.006$) between depression categories for six of eight markers. Adiponectin, leptin, CRP, SAA, apoB, and LDL levels differed by depression category. With the exception of SAA, all were in the expected direction (i.e., a higher depression category was associated with greater metabolic abnormalities or systemic inflammation). For participants with type 1 diabetes, CRP and apoB differed significantly by depression category ($P < 0.006$; leptin, $P = 0.037$; SAA, $P = 0.052$; LDL, $P = 0.054$). In the subsample of participants with type 2 diabetes, no markers differed significantly by depression category (all $P > 0.10$).

After adjustment for demographic and clinical covariates and stratification by diabetes type, all regression models were statistically significant; however, only the apoB model for participants with type 1 diabetes included depression category as a significant correlate ($F[20, 1961] = 26.88$; $P < 0.0001$; $R^2 = 0.22$. No markers were significantly associated with depression among participants with type 2 diabetes. Among youth with type 1 diabetes, those with moderate or severe depression scores (CES-D score ≥24) had apoB levels at 80.9 mg/dL, in contrast to those in the mild depression category (mean of 75.4 mg/dL) and the no or minimal depression category (mean of 75.5 mg/dL).

CONCLUSIONS—The results provide preliminary evidence that higher levels of depression are associated with metabolic abnormalities and systemic inflammation. The proportion of youth with diabetes in this sample who reported clinically significant depressive symptoms (22%) is consistent with population-based reports (9), suggesting that the results may generalize to the larger population. Given the cross-sectional nature of this investigation, however, it is not possible to delineate specific contributions to depression of these biological disruptions versus diabetes, nor the direction of these relationships. In addition, we cannot determine whether there are mutually reinforcing relationships among diabetes, depression, and background metabolic and inflammatory markers, like those suggested in the literature (4,11). These data do, however, shed light on potential pathways and suggest that further, more stringent inquiry is warranted.

For example, after adjustment for demographic and clinical characteristics, the link between higher depression scores

Table 1—*Participant characteristics by diabetes type*

	Overall	Type 1	Type 2
N	2,359	2,007	333
Age (years)	15.2 ± 3.1	15.0 ± 3.1	16.6 ± 2.8
Female sex	1,243 (52.7)	1,025 (51.1)	209 (62.8)
Race or ethnicity			
Non-Hispanic white	1,613 (68.4)	1,531 (76.3)	71 (21.3)
Hispanic	326 (13.8)	243 (12.1)	78 (23.4)
Black/African American	253 (10.7)	148 (7.4)	103 (30.9)
Asian or Pacific Islander	99 (4.2)	63 (3.1)	35 (10.5)
Native American	57 (2.4)	14 (0.7)	43 (12.9)
Other or unknown	11 (0.5)	8 (0.4)	3 (0.9)
Diabetes duration (years)	4.8 ± 4.2	5.2 ± 4.3	2.4 ± 2.0
Hemoglobin A_{1c} (%)	8.4 ± 1.9	8.4 ± 1.7	8.1 ± 2.6
BMI (z score)	0.82 ± 0.97	0.65 ± 0.87	1.87 ± 0.80
Insurance			
Private	1,828 (78.0)	1,640 (82.2)	176 (53.5)
State (Medicaid)	394 (16.8)	279 (14.0)	112 (34.0)
Other	61 (2.6)	37 (1.9)	22 (6.7)
None	61 (2.6)	40 (2.0)	19 (5.8)
CES-D category			
No/minimal	1,832 (77.7)	1,617 (80.6)	202 (60.7)
Mild	328 (13.9)	257 (12.8)	69 (20.7)
Moderate/severe	199 (8.4)	133 (6.6)	62 (18.6)

Data are n (%) or means ± SD, unless otherwise noted.

Table 2—*Metabolic and inflammatory markers by diabetes type and CES-D category*

| | | CES-D category | | |
	Full sample	<16 (no/minimal)	16–23 (mild)	≥24 (moderate/severe)
Type 1 diabetes				
Adiponectin (ng/mL)	17,264 ± 6,802	17,173 ± 6,691	17,868 ± 7,370	17,211 ± 6,985
Leptin (ng/dL)	8.3 ± 9.2	8.3 ± 9.2	8.9 ± 8.6	10.5 ± 10.8
CRP	0.20 ± 0.53	0.19 ± 0.54	0.18 ± 0.34	0.32 ± 0.67
SAA	0.72 ± 2.41	0.73 ± 2.58	0.59 ± 1.17	0.88 ± 2.10
ApoB	77.0 ± 23.3	75.9 ± 22.2	79.5 ± 26.6	86.3 ± 27.1
LPA (nmol/L)	55.3 ± 72.5	53.0 ± 69.1	66.0 ± 84.7	63.2 ± 84.8
IL-6 (pg/mL)	17.7 ± 24.9	17.5 ± 22.6	19.8 ± 38.3	16.2 ± 18.3
LDL	0.278 ± 0.022	0.279 ± 0.021	0.277 ± 0.022	0.274 ± 0.022
Type 2 diabetes				
Adiponectin (ng/mL)	9,618 ± 5,345	9,414 ± 4,883	9,933 ± 5,882	9,932 ± 6,165
Leptin (ng/dL)	23.1 ± 18.8	20.8 ± 16.3	24.9 ± 17.3	28.6 ± 25.6
CRP	0.50 ± 1.00	0.51 ± 1.18	0.54 ± 0.67	0.41 ± 0.52
SAA	0.93 ± 4.00	1.07 ± 5.03	0.77 ± 1.52	0.64 ± 1.02
ApoB	96.0 ± 43.2	93.6 ± 42.8	98.7 ± 31.3	100.6 ± 54.6
LPA (nmol/L)	51.2 ± 63.5	48.6 ± 58.5	52.0 ± 60.9	58.7 ± 80.4
IL-6 (pg/mL)	15.5 ± 26.2	14.1 ± 19.9	19.8 ± 40.6	15.5 ± 23.8
LDL	0.253 ± 0.033	0.254 ± 0.035	0.254 ± 0.027	0.248 ± 0.036

Values are means ± SD in milligrams per deciliter unless otherwise noted.

and higher apoB levels (i.e., dyslipidemia) remained for youth with type 1 diabetes. Those youth in the highest depression category had apoB values 6 mg/dL higher than those with mild to minimal symptoms, and their values were significantly closer to the 100 mg/dL level suggestive of clinical elevation (12). Further, if in future studies the elevation in apoB is confirmed to be attributable to depression, a new modifiable target for intervention (13,14) would be identified.

Recent evidence does point to the immediate and long-term contributions of apoB to both diabetes-related and cardiovascular disease outcomes (15,16). The presence and severity of cardiovascular disease have also been linked with depression through environmental pathways (17,18). Type 1 diabetes thus may be an underlying contributor to the observed emotional and biological disruptions, with depression exacerbating dyslipidemia (12). This may occur through overlapping neuroendocrine pathways or lifestyle behaviors related to diet and physical activity. The fact that apoB came out as the only metabolic marker significantly associated with depression in the multivariate analyses suggest that the relationship between apoB and depression is less affected by mediating influences such as glycemic control and BMI than other by metabolic variables (e.g., LDL) and their relationship with depression.

Similarly, a greater degree of depression was linked with CRP, a measure of systemic inflammation, although this association was no longer evident after adjustment for clinical and demographic factors. These data may indicate an active immune system contributing to the presence of depression. This possibility is supported by the association of circulating proinflammatory cytokines with higher levels of depressive symptoms (5,19). Alternatively, the elevation of CRP may be a result of systemic inflammation resulting from diabetes only, as suggested by a number of studies (7,20).

Nevertheless, the results of this study suggest that further inquiry into the direction and magnitude of the pathways linking depression and diabetes, particularly type 1 diabetes, in youth is warranted. Potential bidirectional or cyclical relationships, which have garnered support in adults (4), also appears worthy of further inquiry. Future studies should aim to investigate these relationships over time, comparing youth in this study with metabolically challenged youth without diabetes to document the influence of diabetes, to examine these relationships in a larger sample of youth with type 2 diabetes, to control for other potentially influential variables such as early indicators of complications, to determine the effects of lowering depression on apoB (and vice versa), and to elucidate the influences of clinical variables (BMI

and hemoglobin A_{1c}) and environmental factors (diet and exercise) on this relationship over time.

References

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1069–1078
2. Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care 2008;31:2398–2403
3. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care 2000;23:934–942
4. Golden SH, Lazo M, Carnethon M, et al. Examining a bidirectional association between depressive symptoms and diabetes. JAMA 2008;299:2751–2759
5. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 2006;27:24–31
6. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 2007;21:153–160
7. Rabinovitch A. An update on cytokines in the pathogenesis of insulin-dependent diabetes mellitus. Diabetes Metab Rev 1998;14:129–151
8. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385–401
9. Rushton JL, Forcier M, Schectman RM. Epidemiology of depressive symptoms in the National Longitudinal Study of Adolescent Health. J Am Acad Child Adolesc Psychiatry 2002;41:199–205
10. Lawrence JM, Standiford DA, Loots B, et al.; SEARCH for Diabetes in Youth Study. Prevalence and correlates of depressed mood among youth with diabetes: the SEARCH for Diabetes in Youth study. Pediatrics 2006;117:1348–1358
11. Lustman PJ, Clouse RE. Depression in diabetes: the chicken or the egg? Psychosom Med 2007;69:297–299
12. Albers JJ, Marcovina SM, Imperatore G, et al. Prevalence and determinants of elevated apolipoprotein B and dense low-density lipoprotein in youths with type 1 and type 2 diabetes. J Clin Endocrinol Metab 2008;93:735–742
13. March J, Silva S, Petrycki S, et al.; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. JAMA 2004;292:807–820
14. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. Psychol Bull 2006;132:132–149
15. Tolonen N, Forsblom C, Thorn L, et al.; FinnDiane Study Group. Lipid abnormalities predict progression of renal disease in patients with type 1 diabetes. Diabetologia 2009;52:2522–2530
16. Guy J, Ogden L, Wadwa RP, et al. Lipid and lipoprotein profiles in youth with and without type 1 diabetes: the SEARCH for Diabetes in Youth case-control study. Diabetes Care 2009;32:416–420
17. Carney RM, Freedland KE. Depression and coronary heart disease: more pieces of the puzzle. Am J Psychiatry 2007;164:1307–1309
18. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med 2002;23:51–61
19. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71:171–186
20. Snell-Bergeon JK, West NA, Mayer-Davis EJ, et al. Inflammatory markers are increased in youth with type 1 diabetes: the SEARCH case-control study. J Clin Endocrinol Metab 2010;95:2868–2876