Higher plasma leptin and lower C-peptide levels are associated with depression: a cross-sectional study

（高い血漿レプチン濃度と低いC-ペプチド濃度はうつと関連している：横断研究）

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Abstract

Background: Depression is a seriously disabling public health problem with very high world-wide prevalence. This study examined cross-sectional association between depression and both inflammatory markers and laboratory data involved in metabolic disturbance among Japanese subjects.

Methods: This cross-sectional study is a secondly analysis for the data of the Iwaki Health Promotion Project 2014 (1167 subjects). Plasma inflammatory markers and laboratory metabolic data involved were used. Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess the prevalence and severity of depressive symptoms. Participants with CES-D scores≥16 were assigned to the 'Depression' group (Group D). Differences between group Non-depression (ND) and D were estimated using χ^2 test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney test for continuous variables. Multivariate logistic regression analysis was also used to identify characteristics, co-morbidities, conditions and laboratory data associated with depression after adjusting for possible confounding factors.

Results: There were significant differences in sex, age, blood pressure, interleukin (IL)-6, fasting blood sugar (FBS), hemoglobin A1c (HbA1c), and cortisol level using univariate analysis between the two groups. However, multivariate logistic regression analysis indicated that lower age, lower C-peptide, and higher leptin were associated with the depression.

Conclusion: This study showed that higher plasma leptin and lower C-peptide levels were significantly associated with depressive symptoms. No significant association was found between plasma inflammatory markers and depressive symptoms after adjusting for possible confounding factors.

Key words: depression, leptin, C-peptide, inflammation

Introduction

Depression is a seriously disabling public health problem with very high world-wide prevalence (1). This psychiatric disease is characterized by the presence of low mood, anhedonia, insomnia, loss of appetite, inattention, and even suicidal ideation/action (2). Moreover, this disorder is independently associated with increased risk of mortality in diabetes, cardiovascular disease, and cancer (3, 4, 5). Thus, novel strategies are needed to detect these patients early and treat appropriately.

Recently, the relationship between inflammatory markers such as interleukin (IL)-6, tumor necrosis factor (TNF)-α and C-reactive protein (CRP) and depression has been reported (6, 7, 8). These studies indicated plasma concentrations of inflammatory markers were elevated in depressive patients. In addition, direct administration of IL-1β and TNF-α to the brain produces depression in rodents (9). On the other hand, a recent community study reported that there are no associations between current depression and plasma CRP levels (10). Therefore, the relationship between inflammatory markers and depression remains controversial.

A bidirectional association between metabolic disturbance and depression has been also reported (11, 12). In particularly, metabolic syndrome is important for its relationship with degenerative and psychiatric disease (13, 14). Although the causal pathways have not been elucidated, energy homeostasis including changes in the hypothalamic-pituitary-adrenal (HPA) axis and glucose metabolism (15) may be involved.

As described above, it remains uncertain whether both inflammatory and metabolic disturbance are associated with depression. If these relationships can be clarified, important questions can be posed regarding pathology and ultimately develop evidence-based treatment. Thus, in this study, we examined the cross-sectional association between depression and both inflammatory and metabolic markers.

Methods

Study procedure and subjects

This cross-sectional study is a secondary analysis of the data of the Iwaki Health Promotion Project 2014 which was approved by the Ethics Committee of the Hirosaki University Graduate School of Medicine. The study included 1167 volunteers living in the Iwaki district of the city of Hirosaki, Japan. All participants in this project gave written informed consent for the publication of the data. Demographic data and medical information were obtained from self-questionnaires and interviews. Blood pressure (BP), height, weight, and waist circumference were measured by health professions. Blood samples were obtained from the medial cubital vein in the sitting position at fasting in the early morning. We measured IL-1β, IL-6, IL-10, TNF-α, Interferon-γ (IFN-γ), leptin, adrenocorticotropic hormone (ACTH), cortisol, triglyceride (TG), total cholesterol (T-cho), fasting blood sugar (FBS), hemoglobin A1c (HbA1c), and C-peptide. We diagnosed metabolic syndrome according to the definition of metabolic syndrome with Japanese criteria 2005 (16): central obesity (waist circumference at umbilical level≥85 cm in male or 90 cm in female) plus more than 2 of the following components-hyperglycemia (FBS≥110 mg/dl), dyslipidemia (TG≥150 mg/dl), and hypertension (systolic blood pressure≥130 mmHg and/or diastolic blood pressure≥85 mmHg). Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess the prevalence and severity of depressive symptoms. This scale is a short self-report scale designed to measure depressive symptomatology in the general population. The maximum score is 60, and higher scores are associated with greater depression. Participants with CES-D scores≥16 were assigned to depression group (group D). Participants in this project were divided into two groups: Non-depression (group ND) and D, and the above variables were compared among groups. We examined any correlations to define a relationship between inflammatory markers and depression, and between laboratory data and depression. We excluded 27 subjects because of missing values.

Measurements of biomarkers

IL-1β, IFN-γ and IL-10 were assayed using an enzyme immunoassay (EIA). IL-6 and TNF-α were assayed using a chemiluminescent EIA. Cortisol and C-peptide were assayed using a chemiluminescent immunoassay (CLI). ACTH was assayed using an electro-CLI. Cortisol and C-peptide were measured using a chemiluminescent immunoassay. Leptin was measured using a radioimmunoassay. All measurements were done by LSI Medience Corporation (Tokyo, Japan). The lower detection limits of IL-1β, IFN-γ, IL-6, IL-10, TNF-α, and leptin were 0.125 pg/ml, 0.156 pg/ml, 0.300 pg/ml, 0.78 pg/ml, 0.55 pg/dl and 0.5 ng/ml, respectively. The upper detection limits of ACTH, cortisol and C-peptide were 2000 pg/ml, 5980 μg/dl and 300 ng/ml, respectively. The maximal intra-assay coefficients of variations were 9.7 % for IL-1β, 7.44 % for IFN-γ, 7.4 % for IL-6, 12.7 % for IL-10, 3.64 % for TNF-α, 2.60 % for ACTH, 10 % for cortisol, 10 % for C-peptide and 5.3 % for leptin.

Statistical analysis

Demographic data, medical information and other variables were presented as median (25th to 75th percentile) and number (a percentage of each group). Statistical differences between the groups ND and D were determined using Chi-squared test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney test for continuous variables. Multivariate logistic regression analysis was also used to identify characteristics, co-morbidities, conditions and laboratory data associated with depression after adjusting for possible covariates. Inclusion of variables in the models was based on existing knowledge that inflammatory markers and metabolic disturbances were associated with depression as described above. Variance Inflation Factor (VIF) was used to check for multicollinearity among each variable. Discrimination was measured with using the area under the curve (AUC). The results were expressed as adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs). All data analysis was performed with GraphPad Prism 7 (GraphPad Software Inc., CA, USA) and EZR software version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). P values<0.05 were considered statistically significant in all tests.

Results

Characteristics of subjects

We analyzed the data of 1140 volunteers; their characteristics are shown in Table 1. There were two subjects treated with antidepressant in the group ND and four subjects in the group D. Univariate analyses showed the following. The prevalence of depression was 24.5 %. There were significantly fewer males and younger subjects in group D than in group ND. In addition, blood pressure was significantly lower in group D than in group ND. However, the multivariate logistic regression analysis indicated that only younger age was associated with depression.

Inflammatory markers and depression

Although univariate analyses showed that plasma IL-6 was significantly lower in group D than group ND (Table 2), multivariate logistic regression analysis showed no significant relationships between plasma IL-6 and depression (Table 3).

Metabolic disturbance and depression

There were significant differences in FBS, HbA1c, and plasma cortisol levels were significantly lower in group D than those in group ND by univariate analyses (Table 2). However, the multivariate logistic regression analysis showed that there were no associations between those variables and depressive symptoms after correction for confounding factors (Table 3). In addition, although there were no significant differences in plasma C-peptide and leptin between groups, the multivariate logistic regression analysis showed that lower plasma levels of C-peptide and higher leptin were associated with depression. However, we could not find an association between depression and metabolic syndrome criteria.

Discussion

In the present study, although univariate analysis suggested significant differences in sex, age, BP,

IL-6, FBS, HbA1c, and cortisol level between two groups, multivariate logistic regression analysis indicated that lower plasma C-peptide, higher plasma leptin and younger age were associated with depression after adjusting for patient characteristics and possible confounding factors.

According to statistics published in 2014 by the Ministry of Health, Labour and Welfare in Japan, depression often develops in 40s (17). Indeed, younger age was associated with depression in the present study.

Recent meta-analysis (18) indicates that there may be an association between inflammatory markers and depression in adults. Chronic neuroinflammation is hypothetically involved in the mechanism of depression. Inflammatory cytokines interact with multiple pathways known to be involved in the development of depression such as monoamine metabolism, neuroendocrine function, synaptic plasticity, and neurocircuits relevant to mood regulation (19). On the other hand, it was reported that there was no association between depression and plasma CRP levels in a cross-sectional analysis of a large cohort from a middle-income country (10). In addition, it was also reported that there was no cross-sectional association between either IL-6, α-1-antichymotrypsin and CRP and depression at baseline, but longitudinal association at 5-year follow-up showed that IL-6 and CRP could be a predictor for depressive symptoms (20). Similarly, multivariate logistic regression analysis showed that there was no association between inflammatory cytokines and development of depression in the present study. Thus, higher plasma inflammatory cytokine levels could reflect peripheral inflammation but may not always neuroinflammation in the brain.

Although previous studies have suggested a significant association between metabolic syndrome and depression (21, 22), the present study did not find any such association. In the present study as we did not assess the influence of treatment of hypertension, diabetes mellitus and dyslipidemia in patients with metabolic syndrome, these might affect the present results. However, we found significant relationships between depression and both leptin and C-peptide that are important biomarkers for metabolic syndrome.

Leptin is an adipokine secreted by adipose tissue, which acts in the mediobasal hypothalamus and regulates energy intake and expenditure through controlling appetite and glucose metabolism (23). It was reported that leptin deficiency or resistance leads to uncontrolled food intake, obesity, and diabetes mellitus (24). Moreover, a previous study showed that diabetic mice with low plasma leptin levels exhibited depression-like behavior and administration of leptin reversed this behavior; leptin may therefore act as an antidepressant (25). Indeed, several cross-sectional studies also demonstrated the associations between plasma leptin levels and depression (26, 27, 28). However, in agreement with the present study, some studies showed high plasma leptin levels areassociated with depression (29, 30, 31). Carvalho et al. (32) performed a systematic review and meta-analysis and found that plasma leptin level was significantly higher in patients with mild/moderate depression when compared to healthy controls but did not differ between patients with severe depression patients and healthy controls. It was likely that in group D most subjects had mild/moderate depression as median CES-D was19 (with 17 to 22 of 25 to 75th percentile).

C-peptide is a 31–amino acid peptide that is cleaved from proinsulin during biosynthesis of insulin (33). As this peptide is produced in equal amounts to insulin, it is used to assess endogenous insulin secretion, including in patients on insulin therapy. Our data demonstrated that lower plasma C-peptide level was associated with depression. Similarly, Jong et al. (34) found a negative correlation between plasma C-peptide and the self-administered Beck Depression Inventory score in patients with maintenance hemodialysis. It is well known that chronic impairment of glucose metabolism is significantly related to depressive disorders (15) and the prevalence of depression is significantly higher in patients with diabetes mellitus (35). In addition, it was reported that downregulation of hypothalamic insulin receptors elicited depressive-like behavior in rats (36). Moreover, not only deficiency of insulin secretion, but also insulin resistance is related to depression. A recent study showed significant relationship between depression and insulin resistance (37). Depressive symptoms often appear at the prediabetes stage characterized by insulin resistance (38). Insulin resistance could

develop because of an increased release of counter-regulatory hormones associated with depression (39). Thus, as insulin may be involved in depression, prevention and treatment of deficiency in insulin secretion and insulin resistance may also improve symptoms of depression.

It has been reported that sex difference likely contributes to the pathophysiology of depressive disorders (40, 27, 41). Indeed, univariate analysis suggests that women showed larger population than men in the present study. However, multivariate logistic regression analysis did not indicate significant factor associated with depression; sample size might be too small to detect significance. This may be one of potential limitations in the present study.

In addition to sample size, the present study has some further limitations. As it was a cross-sectional study, it was difficult to clarify causality between depression and possible confounding factors. As we did not measure depression per se, but depressive symptoms, not all subjects enrolled might have a clinical diagnosis of depression. Indeed, most depressive subjects defined by CED-S score revealed mild/moderate depression without any anti-depressant therapy. Thus, if many severely depressed patients had been included, the conclusion might have changed. Moreover, as this was not a longitudinal study, laboratory data were obtained once.

In conclusion, after adjusting for patient characteristics and possible confounding factors this cross-sectional study showed that higher plasma leptin and lower C-peptide levels were significantly associated with development of depressive symptoms. No significant association was found between plasma inflammatory markers and depressive symptoms. Further studies are required to clarify potential causality between depression and possible confounding factors obtained from the present study such as lower age, lower plasma C-peptide, and higher plasma leptin.

Author' contributions

DT and KH collected and analyzed the data. DT, KH and YN drafted the manuscript. DT, TK, JS, FK, YN, KS and NY-F revised the manuscript. All authors read and approved the final manuscript for submission.

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Table 1. Characteristic of subjects

	Group ND	Group D	P value	T value
N	861	279	-	
Male	343 (39.8 %)	89 (30. 9%)	0.00175*	
Age (year)	58 (44, 66)	52 (37, 65)	0.0019*	
BMI (kg/m^2)	22.5 (20.4, 24.6)	22.2 (20.4, 24.5)	0.292	
SBP (mmHg)	130 (117, 145)	123 (113, 137)	<0.0001*	
DBP (mmHg)	78 (71, 86)	76 (69, 84)	0.0007*	3.42
Waist (cm)	83.7 (77.0, 89.9)	82.2 (76.0 88.8)	0.0638	
Hypertension	227 (26.4 %)	59 (21.2 %)	0.08	
DM	39 (4.53 %)	16(5.73 %)	0.414	
Dyslipidemia	105 (12.2 %)	35 (12.5 %)	0.877	
Stroke	13 (1.50 %)	5 (1.79 %)	0.729	
IHD	15 (1.74 %)	8 (2.87 %)	0.245	
MetS	55 (6.39 %)	13 (4.66%)	0.382	
CES-D	12 (10, 13)	19 (17, 22)	<0.0001*	

Differences between group non-depression (ND) and depression (D) were estimated using Chi-squared test for categorical variables and student's t-test or Mann-Whitney test for continuous variables. Data are shown as number (a percentage of each group) or median (25 to 75th percentile), BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Waist: Waist circumference, DM: Diabetes Mellitus, IHD: Ischemic heart disease, MetS: Metabolic syndrome, *: Statistical significance.

Table 2. Relationships between laboratory data and depression

	Group ND	Group D	P value
IL-1β (pg/mL)	0.205 (0.125, 0.366)	0.230 (0.125, 0.371)	0.428
IL-6 (pg/mL)	0.646 (0.44, 1.01)	0.583 (0.397, 0.979)	0.019*
IL-10 (pg/mL)	0.5 (0.5, 0.77)	0.5 (0.5, 0.8)	0.823
TNF-α (pg/mL)	0.57 (0.55, 0.97)	0.58 (0.55, 0.97)	0.882
IFN-γ (pg/mL)	1.56 (1.56, 1.56)	1.56 (1.56, 1.56)	0.576
Leptin (ng/mL)	4.6 (3, 7.5)	5.1 (2.9, 8.9)	0.144
ACTH (pg/mL)	8.8 (6.7, 11.3)	8.7 (6.7, 10.9)	0.489
Cortisol (μg/dL)	20.2 (12.9, 29.3)	18.6 (12.8, 25.3)	0.048*
TG (mg/dL)	79 (56, 113)	75 (55, 105)	0.106
T-cho (mg/dL)	199 (178, 221)	200 (172, 220)	0.376
FBS (mg/dL)	80 (74, 88)	78(72, 86)	0.036*
HbA1c (%)	5.7 (5.5, 5.9)	5.6 (5.4, 5.8)	0.015*
C-peptide (ng/mL)	0.9 (0.8, 1.2)	0.9 (0.7, 1.1)	0.085

Differences between group non-depression (ND) and depression (D) were estimated using Mann-Whitney test, Data are shown as number (a percentage of each group) or median (25 to 75th percentile), IL: interleukin, TNF: tumor necrosis factor, IFN: interferon, ACTH: adrenocorticotropic hormone, TG: triglyceride, T-cho: total cholesterol, FBS: fasting blood sugar, HbA1C: hemoglobin A1c, *: Statistical significance.

Table 3. Multivariate logistic regression analyses to identify co-morbidities, conditions and laboratory data associated with depression

	OR	95% CI	P value
Male	0.973	0.641-1.480	0.89800
Age (year)	0.985	0.972-0.997	0.01450*
BMI (kg/m2)	1.030	0.943-1.130	0.51000
SBP (mmHg)	0.991	0.979-1.000	0.13300
DPB (mmHg)	0.995	0.977-1.010	0.61700
Waist (cm)	0.991	0.962-1.020	0.55100
Hypertension	0.992	0.662-1.490	0.97000
DM	1.470	0.679-3.200	0.32700
Dyslipidemia	1.210	0.757-1.950	0.42000
Stroke	1.950	0.702-5.440	0.20000
IHD	2.360	0.924-6.010	0.07270
MetS	0.818	0.376-1.780	0.61200
IL-1β (pg/mL)	0.904	0.672-1.220	0.50700
IL-6 (pg/mL)	0.992	0.965-1.020	0.60100
IL-10 (pg/mL	0.992	0.940-1.050	0.75900
TNF-α (pg/mL)	1.070	0.776-1.470	0.69300
IFN-γ (pg/mL)	1.000	0.997-1.000	0.87500
Leptin (ng/mL)	1.050	1.000-1.100	0.03360*
ACTH (pg/mL)	1.020	0.973-1.070	0.42800
Cortisol (μg/dL)	0.992	0.979-1.010	0.26000
TG (mg/dL)	1.000	0.998-1.000	0.93600
T-cho (mg/dL)	1.000	0.997-1.010	0.53100
FBS (mg/dL)	1.000	0.989-1.020	0.57600
HbA1c (%)	1.120	0.754-1.670	0.56900
C-peptide (ng/mL)	0.466	0.275-0.789	0.00451*

As none of the VIF values were up to 10, this indicates that there was no collinearity in the model. AUC value was 0.63. BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Waist: Waist circumference, DM: Diabetes Mellitus, IHD: Ischemic heart disease, MetS: Metabolic syndrome, IL: interleukin, TNF: tumor necrosis factor, IFN: interferon, ACTH: adrenocorticotropic hormone, TG: triglyceride, T-cho: total cholesterol, FBS: fasting blood sugar, HbA1C: hemoglobin A1c, *: Statistical significance.