Tryptophan-kynurenine and lipid related metabolites as blood biomarkers for first-episode drug-na?ve patients with major depressive disorder: An exploratory pilot case-control study

桑野, 信貴

出版情報：Kyushu University, 2018, 博士（医学）, 課程博士
バージョン：
権利関係：

Journal of Affective Disorders 231 (2018) 74–82

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Tryptophan-kynurenine and lipid related metabolites as blood biomarkers for first-episode drug-naïve patients with major depressive disorder: An exploratory pilot case-control study

Nobuki Kuwano[a], Takahiro A. Kato[a,*], Daiki Setoyama[b], Mina Sato-Kasai[a], Norihiro Shimokawa[a], Kohei Hayakawa[a], Masahiro Ohgidani[a], Noriaki Sagata[a], Hiroaki Kubo[a], Junji Kishimoto[c], Dongchon Kang[b], Shigenob Kanba[a]

[a] Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan
[b] Department of Clinical Chemistry and Laboratory Medicine, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan
[c] Department of Research and Development of Next Generation Medicine, Faculty of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan

ARTICLE INFO

Keywords:
First-episode drug-naïve major depressive disorder
Blood biomarkers
Tryptophan-kynurenine metabolites
High density lipoprotein-cholesterol
Cholesteryl esters

ABSTRACT

Background: Early intervention in depression has been critical to prevent its negative impact including suicide. Recent blood biomarker studies for major depressive disorder (MDD) have suggested that tryptophan-kynurenine and lipid related metabolites are involved in the pathophysiology of MDD. However, there have been limited studies investigating these blood biomarkers in first-episode drug-naïve MDD, which are particularly important for early intervention in depression.

Methods: As an exploratory pilot case-control study, we examined the above blood biomarkers, and analyzed how these biomarkers are associated with clinical variables in first-episode drug-naïve MDD patients, based on metabolome/lipidome analysis.

Results: Plasma tryptophan and kynurenine levels were significantly lower in MDD group (N = 15) compared to healthy controls (HC) group (N = 19), and plasma tryptophan was the significant biomarker to identify MDD group (area under the curve = 0.740). Lower serum high density lipoprotein-cholesterol (HDL-C) was the predictive biomarker for severity of depression in MDD group (R^2 = 0.444). Interestingly, depressive symptoms were variously correlated with plasma tryptophan-kynurenine and lipid related metabolites. Moreover, plasma tryptophan-kynurenine metabolites and cholesteryl esters (CEs) were significantly correlated in MDD group, but not in HC group.

Limitations: This study had small sample size, and we did not use the multiple test correction.

Conclusions: This is the first study to suggest that not only tryptophan-kynurenine metabolites but also HDL-C and CEs are important blood biomarkers for first-episode drug-naïve MDD patients. The present study sheds new light on early intervention in clinical practice in depression, and further clinical studies especially large-scale prospective studies are warranted.

1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder, and its prevalence is considered to be 8–12% worldwide (Andrade et al., 2003; Mitchell et al., 2009; Smith, 2014). Patients with MDD show high suicidal risk, severe impairment of social functioning, and cognitive dysfunction (Dong et al., 2017; Kupferberg et al., 2016; Mann et al., 2005; Rosenblat et al., 2015). Early intervention in depression is

Abbreviations: HC, healthy controls; MDD, major depressive disorder; SOD, severity of depression; SCID, Structured Clinical Interview for DSM-IV-TR; BDI-II, Beck Depression Inventory-Second Edition; LC-MS, liquid chromatography-mass spectrometry; Total-C, total-cholesterol; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; Fib, fibrinogen; T-bil, total-bilirubin; D-bil, direct-bilirubin; I-bil, indirect-bilirubin; UA, uric acid; hsCRP, high-sensitivity C-reactive protein; TDO, tryptophan 2,3-dioxygenase; IDO, indoleamine 2,3-dioxygenase; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; PC, phosphatidylcholine; PE, phosphatidylethanolamine; CE, cholesteryl ester; TG, triacylglycerol; ROC curve, receiver operating characteristic curve; AUC, area under the curve; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; BMI, body mass index

* Corresponding author.

https://doi.org/10.1016/j.jad.2018.01.014
Received 17 August 2017; Received in revised form 26 December 2017; Accepted 28 January 2018
Available online 31 January 2018
0165-0327/

critical for effective clinical practice, as longer duration of untreated depression is associated with poorer clinical outcomes including depression-related disability (Ghio et al., 2015). Therefore, early detection of persons with depression is warranted. The Structured Clinical Interview for DSM-IV-TR (SCID) is a well-established structured diagnostic instrument (First et al., 2002). Beck Depression Inventory-Second Edition (BDI-II) is utilized as one of the most reliable self-rated scales to assess severity of depression (SOD) (Beck et al., 1996). Present MDD diagnostic and SOD evaluation systems including SCID and BDI-II completely rely on persons' subjective descriptions, spoken information, and attitudes. As a result, misdiagnoses based on such subjective information are unavoidable (Mitchell et al., 2009). Such difficulties have resulted in confusion in clinical practice (Kato et al., 2016; Kato and Kanba, 2017; Kato et al., 2011b; Kato et al., 2011c). Thus, to resolve the above limitations, the establishment of objective methods to detect persons with depression has been warranted. Biomarkers for MDD have been investigated by various research methods including brain imaging (Gadad et al., 2017; Gururajan et al., 2016; Kunugi et al., 2015). However, to our knowledge, blood biomarkers in practical use for depression have been very limited until now. In order to conduct early intervention in depression more effectively, discovering blood biomarkers for first-episode drug-naïve MDD patients is especially important; yet, many previous studies have included patients under medication and patients with recurrent episodes of MDD.

The tryptophan-kynurenine pathway has recently been highlighted in pathophysiological understanding of MDD beyond the traditional "serotonin hypothesis", based on evidence such as serotonin deficiency by tryptophan reduction, and neurotoxicity due to altered kynurenine metabolites (Dantzer, 2017; Dantzer et al., 2008; Dantzer et al., 2011; Halaris, 2013, 2017; Maes et al., 2012; Maes et al., 2011b; Maes et al., 2009; Myint, 2012; Myint et al., 2007; Myint et al., 2012; Ormstad et al., 2016; Roomruangwong et al., 2017; Schwarcz et al., 2012; Schwarcz and Stone, 2017). On the other hand, a recent study has shown the significance of routine blood biochemical markers including high density lipoprotein-cholesterol (HDL-C) to identify patients with MDD (Peng et al., 2016). Thus, lipid related metabolites have also been suggested to be involved in the pathophysiology of MDD (Liu et al., 2016; Parekh et al., 2017; Shelton and Miller, 2010). Lipid species serve multiple important functions such as membrane composition, energy storage, and signal transduction (Fonteh et al., 2006; Liu et al., 2016; Liu et al., 2015b). However, despite biological significance of lipid species, much remains unknown about lipid species pathophysiology from tryptophan metabolites in MDD. A recent study, using tryptophan hydroxylase-2 knockout mouse, has shown that serotonin deficiency is caused by elevated oxidative stress associated with altered metabolism of serum lipid species (Weng et al., 2016). Thus, we have hypothesized that peripheral lipid species may link with brain systems through tryptophan metabolites in the pathophysiology of MDD.

To our knowledge, blood biomarker studies combining tryptophan metabolites, routine biochemical markers, and lipid species especially focusing on first-episode drug-naïve MDD patients have not existed until now. As an exploratory pilot case-control study between healthy controls (HC) and first-episode drug-naïve MDD patients, we herein investigated blood biomarkers associated with diagnosis, SOD, and depressive symptoms, using a combination of the above blood biomarkers, with metabolome/lipidome analysis. Moreover, we estimated the relationship between tryptophan metabolites and lipid species in MDD.

2. Methods

The present study was approved by the ethics committee of Kyushu University and was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.1. Subjects

Healthy subjects and first-episode drug-naïve MDD patients were enrolled in the present study from May 2014 until December 2015. 19 healthy subjects were selected as HC by interview based on SCID regarding any previous or ongoing psychiatric disorder, physical disorder, and medications, which were set as exclusion criteria. Psychiatric patients were enrolled in Kyushu University Hospital and its related affiliations (mainly outpatients' clinics). The diagnosis of MDD was determined by trained psychiatrists, according to SCID (First et al., 2002). We selected 15 first-episode drug-naïve MDD patients (9 males and 6 females). We confirmed that all the patients have no history of the following diseases; neurodegenerative disorders, bipolar or psychotic disorders, mental retardation, substance abuse, and physical disorders such as cardiovascular disease, liver and kidney disorder, infectious disease, malignancy, and head trauma. All peripheral venous blood samples were collected between 10:00 and 15:00. We did not check as to whether blood samples were collected under fasting or non-fasting conditions, since blood collection of first-episode drug-naïve MDD patients was performed according to the voluntary time when the patients consulted. The plasma and serum were immediately extracted and then frozen and stored at −80 °C until required for analysis. On the day of peripheral venous blood collection, we assessed BDI-II to evaluate SOD and depressive symptoms (Beck et al., 1996). BDI-II is a self-rated scale of depression with relatively many questions on affective and cognitive aspects, which are core features of MDD and are related to negative issues, such as suicide (Beck et al., 1996; Green et al., 2015). In addition, a self-rated scale is useful to conduct early intervention not only in psychiatric settings but also primary care and corporate health settings. Therefore, we selected BDI-II as a rating scale of depression in the present study. The following severity range for BDI-II total score was used to classify SOD: mild depression (14–19); moderate depression (20–28); and severe depression (29–63) (Beck et al., 1996). BDI-II items were assigned to the following sub-categories: "affective" (items "sadness", "loss of pleasure", "crying", and "indecisiveness"), "motivational" (items "pessimism" and "suicidal thoughts"), "cognitive" (items "loss of interest" and "concentration difficulty"), "cognitive distortions" (items "past failure", "guilty feelings", "punishment feelings", "self-dislike", "self-criticalness", and "worthlessness"), "behavioral" (items "agitation", "loss of energy", "irritability", and "tiredness or fatigue"), and "vegetative" (items "changes in sleep", "changes in appetite", and "loss of interest in sex") according to a previous study (Cohen, 2008).

2.2. Routine blood biochemical markers

Routine blood biochemical markers including serum total-cholesterol (Total-C), HDL-C, low density lipoprotein-cholesterol (LDL-C), fibrinogen (Fib), total-bilirubin (T-bil), direct-bilirubin (D-bil), indirect-bilirubin (I-bil), uric acid (UA), and high-sensitivity C-reactive protein (hsCRP) were measured by automatic biochemical analyzer (SRL, Inc., Tokyo, Japan).

2.3. Blood tryptophan metabolites (Metabolomics)

Plasma tryptophan and its related metabolites including tryptophan, serotonin, indoleacetate, indolecarboxaldehyde, kynurenine, kynurenic acid, and xanthurenic acid were measured by liquid chromatography-mass spectrometry (LC-MS) using LCMS-8040 (Shimadzu Corp., Kyoto, Japan), as described previously (Setoyama et al., 2016). Concentration of each plasma metabolite was determined using their standard reagents. Moreover, plasma kynurenine/tryptophan ratio was calculated as an indicator of tryptophan degradation, i.e. an indicator for the activity of tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) (Schrocksnadel et al., 2006).

2.4. Blood lipid species (Lipidomics)

One-microliter of plasma was mixed with 1 mL of methanol. After centrifugation at maximum speed, two-microliter of the supernatant was subjected to LC-MS analysis employing a triple quadrupole mass spectrometer LCMS-8060 (Shimadzu Corp., Kyoto, Japan). High abundant 62 plasma lipid species including lysophosphatidylcholine (LPC), lysophosphatidylethanolamine (LPE), free cholesterol, phosphatidylcholine (PC), phosphatidylethanolamine (PE), cholesteryl ester (CE), and triacylglycerol (TG) were separated by a reverse phase liquid chromatography using a KINETEX 2.6 u C8 100 A column (150 × 2.1 mm, phenomenex). The mobile phase A consisted of 20 mM ammonium formate and the mobile phase B consisted of acetonitril: isopropanol (1:1). Column oven temperature was 40 °C. The gradient elution program was as follows: a flow rate of 0.3 mL/min: 0–1 min, 20%B; 1–2 min, 20–40%B (linear gradient); 2–25 min, 40–92.5%B (non-linear, "shark's fin curve"); 25–26 min, 92.5–100%B (linear gradient); 26–35 min, 100%B; 35–35.1 min, 100–20%B; 35.1–38 min, 20% B. Parameters for positive electrospray ionization mode under multiple reaction monitoring were as follows; drying gas flow rate, 10 L/min; nebulizer gas flow rate, 3 L/min; heating gas flow rate, 10 L/min; interface temperature, 300 °C; DL temperature, 250 °C; and heat block temperature, 400 °C; CID gas, 230kPa. Data processing was essentially as described previously (Setoyama et al., 2016).

2.5. Statistical analysis

The statistical analyses were performed using IBM SPSS Statistics 23.0 (IBM Japan, Ltd., Tokyo, Japan). All results were expressed as mean values (mean ± standard deviation) or median values (median (interquartile range)). The normality of data was tested with Shapiro-Wilk test. To achieve normality, serotonin, indolecarboxaldehyde, xanthurenic acid, Fib, T-Bil, D-Bil, I-Bil, and hsCRP levels were log-transformed. We performed unpaired Student's *t*-test to compare the differences of continuous variables (age and blood biomarker levels), and chi-squared test to compare the proportions of categorical variables (sex) between HC and MDD group. To estimate the diagnostic efficiency of blood biomarkers, we performed canonical discriminant analysis with stepwise selection using diagnosis as the dependent variable, and significant differential blood biomarkers between two groups as explanatory variables. Cross-validation procedure by leave-one out classification was performed in the discriminant analysis with stepwise selection. Moreover, we analyzed the performance of identified blood biomarkers by receiver operating characteristic (ROC) curve. To assess the relationship between blood biomarkers and BDI-II total score, we performed Pearson's correlation analysis for MDD group. To estimate the predictive ability of blood biomarkers for SOD of patients, we performed regression analysis using BDI-II total score as the dependent variable, and blood biomarkers significantly correlated with BDI-II total score as explanatory variables. To assess the relationship between blood biomarkers and scores of BDI-II sub-categories, we performed Spearman's correlation analysis for MDD group due to non-normal distribution for scores of BDI-II sub-categories. To detect plasma lipid species significantly associated with plasma tryptophan metabolites, we performed Pearson's correlation analysis. In this correlation analysis, among plasma tryptophan metabolites, we selected variables significantly correlated with BDI-II total score or scores of BDI-II sub-categories. The threshold for significance was a two-sided P-value < .05.

3. Results

Demographics and clinical variables were described in Table 1. First-episode drug-naïve MDD patients (N = 15) were in acute episode of MDD (disease duration: 4.0 (4.0) weeks). SOD of patients was between moderate to severe in accordance with BDI-II total score (33.1 ± 12.0). There were no significant differences in sex and age between HC and MDD group.

3.1. Comparison of blood biomarker levels

Laboratory characteristics were described in Table 2 and Table S1. Plasma tryptophan and kynurenine levels were significantly lower in MDD group compared to HC group (P = .010, P = .018, respectively).

3.2. Diagnostic efficiency of blood biomarkers

Stepwise selection of the discriminant analysis between HC and MDD group was performed to estimate the diagnostic efficiency using plasma tryptophan and kynurenine. Plasma tryptophan was selected as the biomarker significantly associated with MDD diagnosis through the stepwise selection (P = .010). The discriminant function was significant (F = 7.533, df_1 = 1, df_2 = 32, P = .010), and calculated for the assessment of MDD group as follows: D = − 5.650 + 0.393 (tryptophan) (HC group: D > 0, MDD group: D < 0). The correct classification rate obtained from discriminant analysis between HC and MDD group was 76.5%, with a sensitivity and specificity of 80.0% and 73.7%, respectively. To estimate the diagnostic performance of plasma tryptophan, the area under the curve (AUC) was calculated by ROC curve. Plasma tryptophan exhibited an AUC of 0.740 (95% confidence interval = 0.565–0.916, P = .018) (Fig. S1).

3.3. Relationship between blood biomarkers and SOD

As shown in Table S2, serum HDL-C was negatively correlated with BDI-II total score (r = −0.666, P = .007). Moreover, we performed single linear regression analysis to predict BDI-II total score of patients based on serum HDL-C. The significant regression equation was found (F (1, 13) = 10.381, R^2 = 0.444, P = .007), as follows: predicted BDI-II total score of patients = 78.994 − 0.702 (HDL-C) (Fig. 1). Moreover, to control the above regression analysis by age and sex, we performed multiple linear regression analysis using BDI-II total score as the dependent variable, and HDL-C, age, and sex as explanatory variables with forced entry. After control by age and sex, serum HDL-C still exhibited a significant predictive ability of SOD (partial correlation coefficient = −0.619, t = −2.611, P = .024).

3.4. Relationship between blood biomarkers and depressive symptoms

As shown in Table 3 and Table S3, there was positive correlation between (1) plasma tryptophan and "motivational" symptoms such as suicidal thoughts, and (2) serum LDL-C and "vegetative" symptoms such as changes in appetite; negative correlation between (3) plasma kynurenic acid and "vegetative" symptoms, (4) plasma kynurenine/tryptophan ratio and "motivational" symptoms, and (5) serum HDL-C and various depressive sub-symptoms especially "affective" symptoms such as sadness and loss of pleasure. Moreover, as shown in Table S4, several plasma lipid species were significantly correlated with depressive sub-symptoms. In particular, plasma CE 20:0 and CE 20:1 were negatively correlated with depressive sub-symptoms such as "motivational" symptoms including suicidal thoughts.

3.5. Relationship between blood tryptophan metabolites and lipid species

As shown in Fig. 2 and Table S5, several plasma CEs including CE 20:0 and CE 20:1 were significantly correlated with plasma tryptophan and kynurenic acid in MDD group. On the other hand, the above significant correlation between plasma tryptophan-kynurenine metabolites and lipid species in MDD group was not detected in HC group (Fig. S2 and Table S6).

Table 1
Demographics and clinical variables of healthy controls and first-episode drug-naïve MDD patients.

Demographics	**Healthy controls**		**First-episode drug-naïve MDD patients**		**Statistics**	**df**	**P-value**
N (Male/Female)	19 (10/9)		15 (9/6)		χ^2 = 0.185	1	0.667
	Mean	**S.D.**	**Mean or (Median)**	**S.D. or (IQR)**	**Statistics**	**df**	**P-value**
Age (year)	30.2	6.8	30.1	7.6	t = 0.058	32	0.954
Disease duration (week)	–	–	(4.0)	(4.0)	–	–	–
Clinical variables	**Mean**	**S.D.**	**Mean**	**S.D.**	**Statistics**	**df**	**P-value**
BDI-II total score	–	–	33.1	12.0	–	–	–

Statistical P-values were derived from chi-squared test and Student's *t*-test.
Abbreviations: MDD, major depressive disorder; IQR, interquartile range.
BDI-II, Beck Depression Inventory-Second Edition.

Table 2
Comparison of blood biomarker levels between healthy controls and first-episode drug-naïve MDD patients.

Blood biomarkers	**Healthy controls (N = 19)**		**First-episode drug-naïve MDD patients (N = 15)**		**Statistics**		
	Mean	**S.D.**	**Mean**	**S.D.**	**t**	**df**	**P-value**
Tryptophan (μM)	**15.43**	**2.37**	**13.02**	**2.75**	**2.745**	**32**	**0.010**
Log serotonin (μM)	−3.60	0.61	−3.74	1.58	0.357	32	0.723
Indoleacetate (μM)	0.107	0.053	0.111	0.040	−0.247	32	0.807
Log indolecarboxaldehyde (μM)	−5.29	0.37	−5.49	0.43	1.446	32	0.158
Kynurenine (μM)	**0.127**	**0.033**	**0.097**	**0.035**	**2.498**	**32**	**0.018**
Kynurenic acid (μM)	0.0032	0.0016	0.0030	0.0013	0.348	32	0.730
Log xanthurenic acid (μM)	−7.71	0.68	−7.36	1.16	−1.094	32	0.282
Kynurenine/tryptophan ratio	0.0084	0.0026	0.0075	0.0026	0.966	32	0.341
Total-C (mg/dL)	183.5	41.7	175.1	25.8	0.682	32	0.500
HDL-C (mg/dL)	66.11	14.53	65.33	11.36	0.169	32	0.867
LDL-C (mg/dL)	117.4	43.8	109.8	24.0	0.605	32	0.549
Log Fib (mg/dL)	5.48	0.26	5.44	0.20	0.515	32	0.610
Log T-Bil (mg/dL)	−0.53	0.48	−0.56	0.41	0.236	32	0.815
Log D-Bil (mg/dL)	−1.68	0.45	−1.71	0.40	0.245	32	0.808
Log I-Bil (mg/dL)	−0.92	0.51	−0.95	0.44	0.199	32	0.843
UA (mg/dL)	5.09	1.20	5.03	1.10	0.153	32	0.879
Log hsCRP (ng/dL)	5.66	1.36	5.18	1.01	1.150	32	0.259

Statistical P-values were derived from Student's *t*-test.
Significant P-values are shown in bold type.
Abbreviations: MDD, major depressive disorder; Total-C, total-cholesterol.
HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; Fib, fibrinogen.
T-bil, total-bilirubin; D-bil, direct-bilirubin; I-bil, indirect-bilirubin; UA, uric acid.
hsCRP, high-sensitivity C-reactive protein.

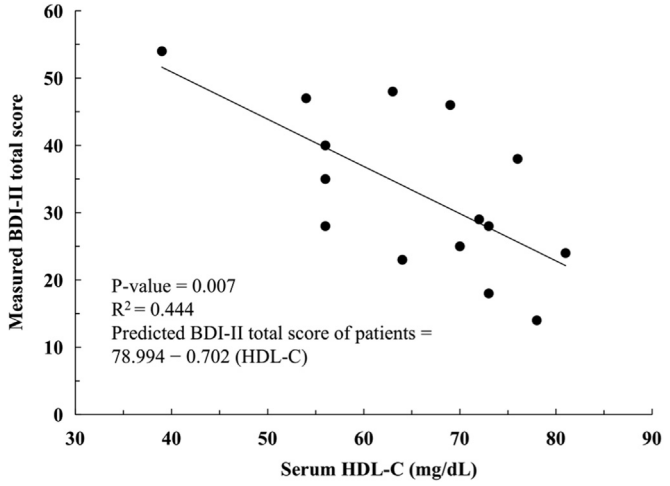

Fig. 1. Single linear regression model of measured BDI-II total score on serum HDL-C in first-episode drug-naïve MDD patients. A linear regression line with dot plots showing serum HDL-C levels and measured BDI-II total score of patients (N = 15). Abbreviations: MDD, major depressive disorder; BDI-II, Beck Depression Inventory-Second Edition; HDL-C, high density lipoprotein-cholesterol.

Table 3
Significant relationship between blood biomarkers and scores of BDI-II sub-categories in first-episode drug-naïve MDD patients (N = 15).

BDI-II sub-categories	**Blood biomarkers**	ρ	**P-value**
"Affective" symptoms (sadness, loss of pleasure, etc.)	HDL-C (mg/dL)	−0.843	< 0.001
"Motivational" symptoms (suicidal thoughts, etc.)	Tryptophan (μM)	0.540	0.038
	Kynurenine/tryptophan ratio	−0.555	0.032
"Cognitive distortions" symptoms (guilty feelings, worthlessness, etc.)	HDL-C (mg/dL)	−0.545	0.036
"Behavioral" symptoms (agitation, loss of energy, etc.)	HDL-C (mg/dL)	−0.676	0.006
"Vegetative" symptoms (changes in appetite, etc.)	Kynurenic acid (μM)	−0.527	0.043
	LDL-C (mg/dL)	0.577	0.024

Statistical P-values were derived from Spearman's correlation analysis.
Abbreviations: MDD, major depressive disorder; BDI-II, Beck Depression Inventory-Second Edition.
HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol.

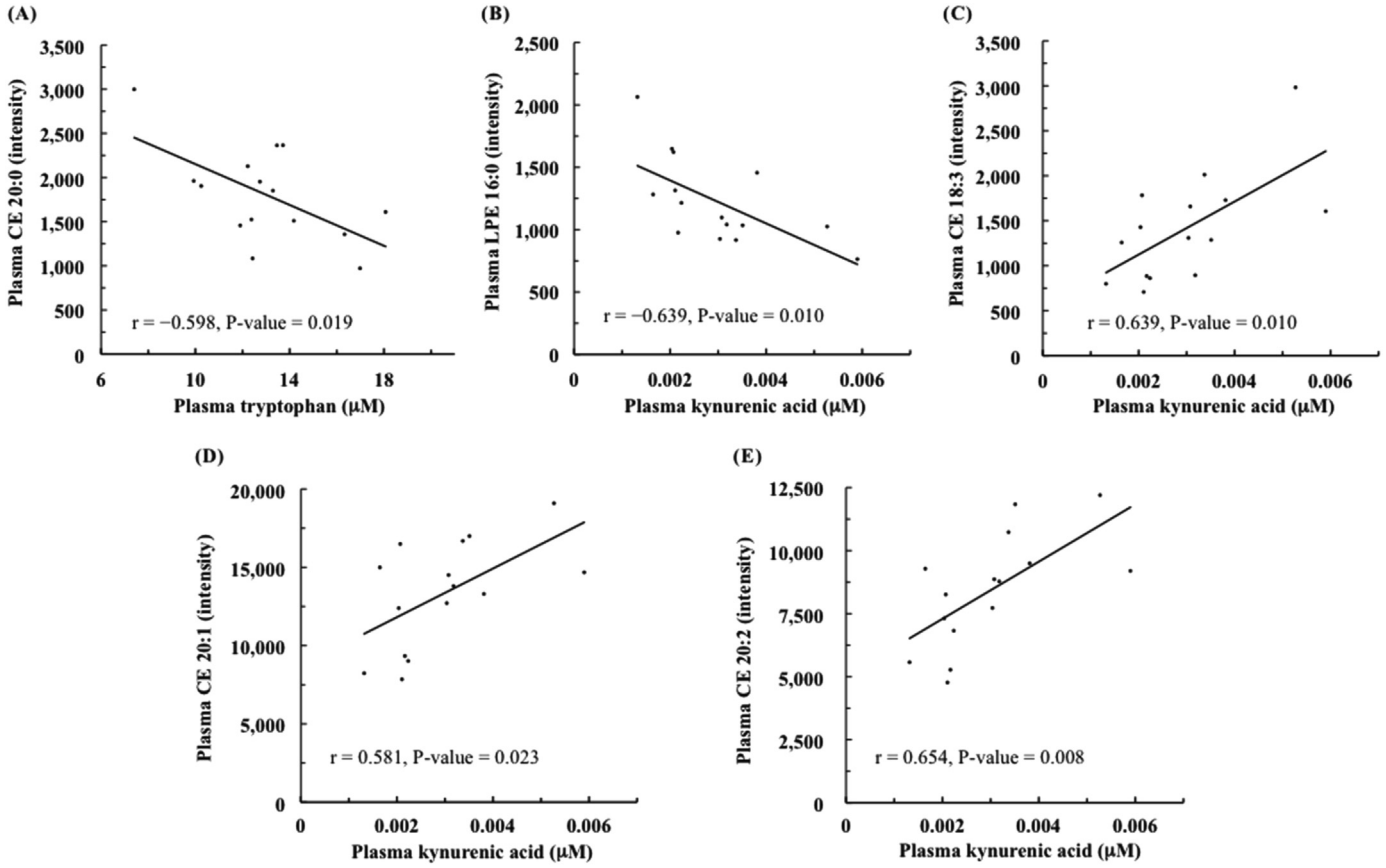

Fig. 2. Scatter plot showing significant relationship between plasma tryptophan metabolites and lipid species in first-episode drug-naïve MDD patients. Linear regression lines with dot plots showing **(A)** plasma tryptophan and CE 20:0 levels, **(B)** plasma kynurenic acid and LPE 16:0 levels, **(C)** plasma kynurenic acid and CE 18:3 levels, **(D)** plasma kynurenic acid and CE 20:1 levels, and **(E)** plasma kynurenic acid and CE 20:2 levels in patients (N = 15). Statistical P-values derived from Pearson's correlation analysis. Abbreviations: MDD, major depressive disorder; LPE, lysophosphatidylethanolamine; CE, cholesteryl ester.

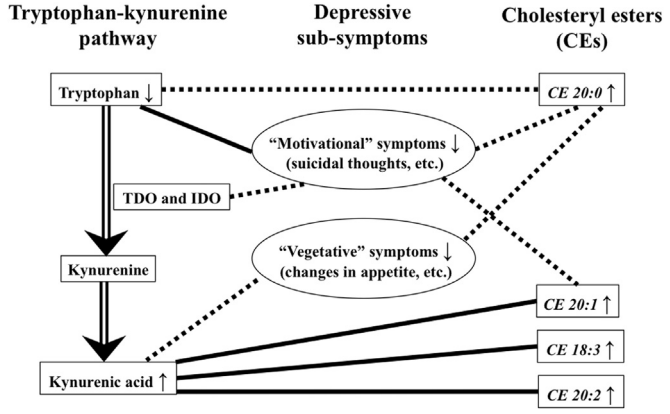

Fig. 3. Scheme: Relationships between tryptophan metabolites, lipid species, and depressive symptoms in first-episode drug-naïve MDD patients. Solid lines showing positive correlation, and dot lines showing negative correlation. Narrow arrows following above variables, showing correlation between variables, for example higher plasma CE 20:0 levels during lower plasma tryptophan levels. Box frames showing metabolites (lipid species shown in italic type), and round frames showing BDI-II sub-categories. Wide arrows showing tryptophan-kynurenine pathway. Abbreviations: MDD, major depressive disorder; BDI-II, Beck Depression Inventory-Second Edition; TDO, tryptophan 2,3-dioxygenase; IDO, indoleamine 2,3-dioxygenase; CE, cholesteryl ester.

4. Discussion

This is the first blood biomarker study combining tryptophan metabolites, routine biochemical markers, and lipid species in first-episode drug-naïve MDD patients. In this exploratory pilot study, plasma tryptophan and kynurenine levels were significantly lower in MDD group compared to HC group; plasma tryptophan exhibited a moderate predictive ability of diagnosis in the discriminant analysis and ROC curve. SOD (BDI-II total score) was negatively correlated with serum HDL-C in MDD group; serum HDL-C exhibited a moderate predictive ability of SOD in linear regression analysis. In addition, severities of depressive sub-symptoms (based on scores of BDI-II sub-categories) were variously correlated with plasma tryptophan-kynurenine and lipid related metabolites. Moreover, plasma tryptophan-kynurenine metabolites and CEs were significantly correlated in MDD group, but not in HC group. We have summarized the present findings in Fig. 3.

Supporting the present results, a meta-analysis study has shown reduced plasma tryptophan levels in patients with MDD, particularly in unmedicated patients (Ogawa et al., 2014). Clinical studies measuring plasma tryptophan levels in first-episode drug-naïve MDD patients are limited, while some previous studies have also shown reduced plasma tryptophan levels in first-episode drug-naïve MDD patients (Liu et al., 2015b; Xu et al., 2012). Recent evidence including our present data has offered a potential utility for measuring plasma tryptophan as an objective tool for supporting diagnosis of MDD patients in clinical practice, especially for early intervention.

The "serotonin hypothesis" detailing serotonin-system dysfunction in the brain has been a central and longstanding hypothesis of depression (Coppen, 1967; Fava and Kendler, 2000; Oxenkrug, 2013). Serotonin synthesis in the brain is considerably dependent on the availability to deliver an adequate volume of tryptophan, a precursor for serotonin, from blood to the brain (Fernstrom, 1977). Lower volume of serotonin in the brain after tryptophan depletion has been suggested to lead to depressive symptoms (Young, 2013; Young et al., 1985).

Several studies have shown altered regulation of serotonin-2 receptors in response to tryptophan depletion (Price et al., 1997; Yatham et al., 2012). In addition, there has been some evidence showing the effect of tryptophan loading as a treatment for depression (Parker and Brotchie, 2011). The present results and recent evidence suggest that tryptophan supplementation may improve patients with depression.

In the reconstruction of the conventional serotonin hypothesis of depression, a secondary metabolic pathway of tryptophan, called tryptophan-kynurenine pathway, has recently attracted attention (Dantzer, 2017; Dantzer et al., 2008; Dantzer et al., 2011; Halaris, 2013, 2017; Maes et al., 2012; Maes et al., 2011b; Maes et al., 2009; Myint, 2012; Myint et al., 2007; Myint et al., 2012; Ormstad et al., 2016; Roomruangwong et al., 2017; Schwarcz et al., 2012; Schwarcz and Stone, 2017). Lower kynurenic acid, a kynurenine-pathway metabolite, is suggested to lead to lower neuroprotective activity, since kynurenic acid is an antagonist of N-methyl-d-aspartate receptors and alpha7-nicotinylcholine receptors (Dantzer et al., 2011; Maes et al., 2011b; Myint, 2012; Myint et al., 2012; Schwarcz et al., 2012; Schwarcz and Stone, 2017). In the present study, we have shown positive correlation between plasma tryptophan and "motivational" symptoms including suicidal thoughts, and negative correlation between plasma kynurenic acid and "vegetative" symptoms. The activation of TDO and IDO, which degrades tryptophan to kynurenine along this pathway, is suggested to reduce serotonin production through upregulation of tryptophan degradation, and such imbalance of tryptophan-kynurenine pathway is suggested to be involved in the development of depression (Dantzer et al., 2011; Halaris et al., 2015; Maes et al., 2012; Maes et al., 2011b; Myint, 2012; Myint et al., 2012). In the present study, there has been no significant difference in the plasma kynurenine/tryptophan ratio, an indicator for the activity of TDO and IDO, between HC and MDD group. However, we have shown that plasma kynurenine/tryptophan ratio is negatively correlated with "motivational" symptoms including suicidal thoughts. On the other hand, a previous study has shown that plasma tryptophan levels and activity of TDO and IDO are elevated in MDD patients with a history of suicide attempts (Sublette et al., 2011). Several previous reports have suggested the upregulation of tryptophan-kynurenine pathway in suicidality, while other reports have suggested contradictory findings (Bay-Richter et al., 2015; Brundin et al., 2016; Busse et al., 2015; Setoyama et al., 2016). Further clinical studies especially longitudinal studies should be conducted to clarify how tryptophan-kynurenine pathway contributes to the underlying mechanisms of suicidality. Substances not measured in the present study are neurotoxic kynurenine-pathway metabolites such as 3-hydroxykynurenine and quinolinic acid that have been suggested to be important for further understanding of imbalance of tryptophan-kynurenine pathway in MDD (Dantzer et al., 2011; Halaris et al., 2015; Steiner et al., 2011). In addition, inflammation is deeply involved with both MDD and tryptophan-kynurenine pathway, while we did not measure inflammatory markers except for hsCRP. Proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are known to activate IDO, as a result, inhibit biosynthesis from tryptophan to serotonin (Dantzer et al., 2011; Halaris et al., 2015; Maes et al., 2012; Maes et al., 2011b; Myint, 2012; Myint et al., 2012). Moreover, many studies have reported that brain inflammation through proinflammatory cytokines, etc., plays an important role in the pathophysiology of MDD, and that enhanced neurodegeneration in MDD may be caused by inflammatory processes (Dantzer et al., 2008; Goldsmith et al., 2016; Halaris, 2013, 2017; Maes et al., 2009). Further studies combining inflammatory markers, such as IL-6 and TNF-α, and tryptophan-kynurenine metabolites including 3-hydroxykynurenine and quinolinic acid should be conducted to reveal the underlying relationships between MDD, inflammation, and tryptophan-kynurenine pathway.

Blood cholesterols such as HDL-C and LDL-C have been suggested to be involved in the pathophysiology of MDD (Parekh et al., 2017; Shelton and Miller, 2010). To our knowledge, this is the first study to suggest that serum HDL-C is negatively correlated with SOD in first-episode drug-naïve MDD patients. Based on the present results, we have proposed lower serum HDL-C as a predictive blood biomarker of SOD especially for first-episode drug-naïve MDD patients. Supporting the present study, several studies have reported that serum HDL-C is negatively correlated with SOD in patients with MDD (Lucka et al., 2017; Shin et al., 2008). HDL-C is known to be carried by a lipoprotein, HDL (Camont et al., 2011). HDL possesses antioxidative properties by protecting LDL from oxidative damage induced by free radicals, etc., and through removal of oxidised lipids from oxidised LDL with subsequent inactivation (Camont et al., 2011). Moreover, HDL also inhibits intracellular generation of reactive oxygen species (Camont et al., 2011). Therefore, HDL-C levels may be expressive of HDL antioxidative activities (Liu et al., 2015a). On the other hand, oxidative stress is known to cause cellular damage such as lipid peroxidation, enzyme inactivation, and DNA modification (Fridovich, 1986). Moreover, oxidative stress is suggested to disrupt the blood-brain-barrier, allowing neuropathological species such as proinflammatory cytokines to enter the brain (Halliwell, 2006; Najjar et al., 2013). Many studies have shown elevated oxidative stress in patients with MDD (Herken et al., 2007; Liu et al., 2015a; Maes et al., 2010), thus oxidative stress is regarded to be involved in the pathophysiology of MDD (de Melo et al., 2017; Maes et al., 2011a; Michel et al., 2012). Interestingly, the antidepressant effect of omega-3 fatty acids is suggested to be partly associated with improvement of HDL function relevant to the upregulation of antioxidative activity (Burillo et al., 2012; Grosso et al., 2014). Thus, we have hypothesized that the downregulation of antioxidative activity due to lower serum HDL-C levels may lead to increased SOD, and that HDL-C may work as an antidepressant through antioxidative activity.

The present metabolome/lipidome analysis has revealed that plasma lipid species such as LPCs, PCs, PEs, CEs, and TGs are variously correlated with several depressive sub-symptoms. These lipid species provide important biological functions such as membrane structure, energy storage, and signal transduction, and act as a cellular mediator (Fonteh et al., 2006; Liu et al., 2016; Liu et al., 2015b). Therefore, lipid species have been suggested to enhance existing knowledge of brain diseases including MDD (Fonteh et al., 2006; Liu et al., 2016; Liu et al., 2015b). Interestingly, the present study has shown that some plasma CEs are negatively correlated with "motivational" symptoms including suicidal thoughts. Supporting the present results, meta-analysis studies have suggested that serum cholesterol is negatively associated with suicidality (Muldoon et al., 1990; Wu et al., 2016). CEs, formed by the esterification of cholesterol, play an important part in cholesterol transportation and homeostasis (Tosi and Tugnoli, 2005). Through esterification of cholesterol, blood cholesterol is transported in blood by lipoproteins such as HDL and LDL, and can be accumulated and utilized in cells (Camont et al., 2011; Tosi and Tugnoli, 2005). Moreover, cholesterol serves multiple important functions such as maintenance of plasma membrane fluidity, neurogenesis, and transmembrane protein and receptor activity (Fonteh et al., 2006). Therefore, changes in cholesterol metabolism significantly modulate brain function (Fonteh et al., 2006). Based on the above, we propose that lower esterification in cholesterol may constitute the pathophysiology of MDD through altered plasma membrane fluidity and receptors function such as serotonin receptor (Heron et al., 1980; Maes et al., 1994).

How peripheral cholesterol influences brain systems is unclear, due to the inability of cholesterol to cross the blood–brain-barrier (Parekh et al., 2017). On the other hand, a recent clinical study has shown that cholesterol-lowering treatment leads to downregulation of tryptophan-kynurenine pathway paralleled by oxidative stress improvement in patients with chronic kidney disease (Zinellu et al., 2015). Moreover, a recent rodent study has shown that serum lipid species are involved with altered function of tryptophan metabolites (Weng et al., 2016). Thus, we have hypothesized that other than the above-discussed relationship between HDL-C and oxidative stress, the relationship between peripheral tryptophan metabolites and CEs may explain how

peripheral cholesterol effects brain activities. Supporting our hypothesis, the present study has shown that plasma tryptophan levels are lower and plasma kynurenic acid levels are higher during higher plasma CEs levels in patients with MDD, but not in HC. In addition, the present study has shown that such alteration of the above substances is significantly associated with lower depressive symptoms (Fig. 3). While peripheral kynurenic acid mostly does not cross the blood-brain-barrier (Nemeth et al., 2005), peripheral kynurenic acid may be involved in the pathophysiology of MDD through its antioxidative activity on reactive oxygen species (Lugo-Huitron et al., 2011). Therefore, plasma CEs may link with brain systems through the antioxidative activity of plasma kynurenic acid, which may be involved in the pathophysiology of MDD. Both tryptophan-kynurenine metabolites and cholesterol have been suggested to be involved in inflammation (Dantzer, 2017; Dantzer et al., 2011; Halaris et al., 2015; Maes et al., 2012; Maes et al., 2011b; Myint, 2012; Myint et al., 2012; Parekh et al., 2017). Brain inflammation induced by microglial activation is now highlighted in various psychiatric disorders including MDD (Hayakawa et al., 2014; Horikawa et al., 2010; Kato et al., 2011a; Kato et al., 2013; Monji et al., 2009; Ohgidani et al., 2016; Sato-Kasai et al., 2016). Further studies are needed to clarify the interactions between tryptophan-kynurenine metabolites, cholesterol, CEs, inflammation, and microglial activation by utilizing cross-species studies with animal models of depression and patients with depression.

4.1. Limitations

The present exploratory pilot study has some limitations. First, the main limitation is sample size. Small sample size has its restriction in drawing conclusive findings, and the present findings are preliminary. In addition, we did not use multiple test correction to avoid the risk of false negatives, as the purpose of this study was the global analysis of a number of blood biomarkers as an exploratory pilot study for a future validation study. Despite the small sample size, we have successfully detected several statistically significant data. Since candidate biomarkers have been identified, follow-up studies with greater sample size should be conducted to validate our preliminary findings. Machine learning is known to be a useful technique to evaluate the validity of the results in biomarker studies (Angermueller et al., 2016). Thus, in the future validation studies, machine learning should be conducted to improve the quality of research. On the other hand, low statistical power due to small sample size of the present study led to the lack of significance in many substances. One of these substances is CRP with accumulated evidence that CRP is higher in patients with MDD (Haapakoski et al., 2015; Howren et al., 2009). In addition, Maes and his colleagues have investigated the action of xanthurenic acid, one of the final metabolites in tryptophan-kynurenine pathway, and have suggested that xanthurenic acid is involved with psychiatric disorders including depression through an anti-inflammatory effect (Kanchanatawan et al., 2017; Maes et al., 1986; Maes et al., 2007). However, as mentioned above, the present findings are preliminary, since drawing conclusive findings is difficult due to small sample size. In addition, the levels of some blood biomarkers may change according to the stage of MDD. Further longitudinal studies with greater sample size should be conducted. Second, the disease specificity of biomarkers is a critical issue in the present study. Tryptophan, kynurenine metabolites, and CEs have been reported to be involved not only with MDD but also with various psychiatric disorders such as schizophrenia and bipolar disorder and physical disorders such as inflammatory bowel diseases, infectious diseases, and heart diseases (Choi et al., 2017; Dantzer et al., 2011; Halaris, 2013, 2017; Maes et al., 2011b; Martin-Subero et al., 2016; Murakami et al., 2013; Myint, 2012; Schwarcz et al., 2012; Sorci-Thomas and Thomas, 2016). Interestingly, depression, or at least some depressive symptoms, also occur in the above disorders. Therefore, the candidate biomarkers in the present study may be common biomarkers for depressive symptoms in various psychiatric and physical disorders. An integrative approach towards depression in various diseases is warranted to search for common biomarkers for depressive symptoms beyond the boundaries of certain diseases. Third, we did not assess body mass index (BMI) and diet conditions. Levels of some blood biomarkers are affected by BMI and diet. Further studies should check BMI and as to whether blood samples were collected under fasting or non-fasting conditions. Fourth, in the exclusion criteria of HC, we did not check psychiatric and physical disorders in first degree relatives. Levels of some blood biomarkers may be affected by family history, especially by family history of diseases with genetic predisposition. Further studies should check psychiatric and physical disorders of the first degree relatives of HC.

4.2. Conclusion

In the present study, we have shown the first findings that not only tryptophan-kynurenine metabolites but also HDL-C and CEs are important blood biomarkers for first-episode drug-naïve MDD patients. The present study has shed new light on the role of tryptophan-kynurenine and lipid related metabolites in the pathophysiology of MDD. The diagnosis and symptom evaluation of MDD in clinical practice has depended on physician's clinical experiences and patient's self-assessments. As a result, there are many delayed consultations and treatments, and misdiagnoses. The blood biomarkers proposed in the present study are possible objective diagnostic indicators for first-episode drug-naïve patients with depression, which are particularly important and useful for early detection not only in psychiatric settings but also primary care and corporate health settings. The present findings are expected to be validated by larger population studies combining with machine learning technique. In addition, further studies should evaluate whether the present findings can be also applied to other situations, such as prognosis evaluation and patients under medication.

Acknowledgments

The authors would like to thank Dr. Koji Tanaka, Mr. Keita Kurahara, Ms. Ryoko Katsuki, and Ms. Sakumi Kakimoto for their research support and/or assistance.

Role of funding source

This work was partially supported by Grant-in-Aid for Scientific Research on (1) Innovative Areas “Will-Dynamics” and "Glia Assembly" of The Ministry of Education, Culture, Sports, Science, and Technology, Japan (JP16H06403 to T.A.K.; JP25117011 to S.K.), (2) The Japan Agency for Medical Research and Development (AMED) (Syogaisya-Taisaku-Sogo-Kenkyu-Kaihatsu-Jigyo to T.A.K. & S.K. (16dk0307047h0002), and Yugo-no to T.A.K. (16dm0107095h0001)), (3) KAKENHI - the Japan Society for the Promotion of Science (JP26713039, JP15K15431, & JP16H03741 to T.A.K., and JP16H02666 to S.K.), and (4) SENSHIN Medical Research Foundation (to T.A.K. and S.K.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2018.01.014.

References

Andrade, L., Caraveo-Anduaga, J.J., Berglund, P., Bijl, R.V., De Graaf, R., Vollebergh, W., Dragomirecka, E., Kohn, R., Keller, M., Kessler, R.C., Kawakami, N., Kilic, C., Offord, D., Ustun, T.B., Wittchen, H.U., 2003. The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE)

Surveys. Int. J. Methods Psychiatr. Res. 12, 3–21.
Angermueller, C., Parnamaa, T., Parts, L., Stegle, O., 2016. Deep learning for computational biology. Mol. Syst. Biol. 12, 878.
Bay-Richter, C., Linderholm, K.R., Lim, C.K., Samuelsson, M., Traskman-Bendz, L., Guillemin, G.J., Erhardt, S., Brundin, L., 2015. A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality. Brain. Behav. Immun. 43, 110–117.
Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for Beck Depression Inventory-Second Edition. The Psychological Corporation, San Antonio.
Brundin, L., Sellgren, C.M., Lim, C.K., Grit, J., Palsson, E., Landen, M., Samuelsson, M., Lundgren, K., Brundin, P., Fuchs, D., Postolache, T.T., Traskman-Bendz, L., Guillemin, G.J., Erhardt, S., 2016. An enzyme in the kynurenine pathway that governs vulnerability to suicidal behavior by regulating excitotoxicity and neuroinflammation. Transl. Psychiatry 6, e865.
Burillo, E., Mateo-Gallego, R., Cenarro, A., Fiddyment, S., Bea, A.M., Jorge, I., Vazquez, J., Civeira, F., 2012. Beneficial effects of omega-3 fatty acids in the proteome of high-density lipoprotein proteome. Lipids Health Dis. 11, 116.
Busse, M., Busse, S., Myint, A.M., Gos, T., Dobrowolny, H., Muller, U.J., Bogerts, B., Bernstein, H.G., Steiner, J., 2015. Decreased quinolinic acid in the hippocampus of depressive patients: evidence for local anti-inflammatory and neuroprotective responses? Eur. Arch. Psychiatry Clin. Neurosci. 265, 321–329.
Camont, L., Chapman, M.J., Kontush, A., 2011. Biological activities of HDL subpopulations and their relevance to cardiovascular disease. Trends Mol. Med. 17, 594–603.
Choi, S.H., Sviridov, D., Miller, Y.I., 2017. Oxidized cholesteryl esters and inflammation. Biochim. Biophys. Acta 1862, 393–397.
Cohen, A., 2008. The underlying structure of the Beck Depression Inventory II: a multidimensional scaling approach. J. Res. Pers. 42, 779–786.
Coppen, A., 1967. The biochemistry of affective disorders. Br. J. Psychiatry 113, 1237–1264.
Dantzer, R., 2017. Role of the Kynurenine metabolism pathway in inflammation-induced depression: preclinical approaches. Curr. Top. Behav. Neurosci. 31, 117–138.
Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci. 9, 46–56.
Dantzer, R., O'Connor, J.C., Lawson, M.A., Kelley, K.W., 2011. Inflammation-associated depression: from serotonin to kynurenine. Psychoneuroendocrinology 36, 426–436.
de Melo, L.G.P., Nunes, S.O.V., Anderson, G., Vargas, H.O., Barbosa, D.S., Galecki, P., Carvalho, A.F., Maes, M., 2017. Shared metabolic and immune-inflammatory, oxidative and nitrosative stress pathways in the metabolic syndrome and mood disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 78, 34–50.
Dong, M., Wang, S.B., Li, Y., Xu, D.D., Ungvari, G.S., Ng, C.H., Chow, I.H.I., Xiang, Y.T., 2017. Prevalence of suicidal behaviors in patients with major depressive disorder in China: a comprehensive meta-analysis. J. Affect. Disord. 225, 32–39.
Fava, M., Kendler, K.S., 2000. Major depressive disorder. Neuron 28, 335–341.
Fernstrom, J.D., 1977. Effects on the diet on brain neurotransmitters. Metabolism 26, 207–223.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). Biometrics Research, New York State Psychiatric Institute, New York.
Fonteh, A.N., Harrington, R.J., Huhmer, A.F., Biringer, R.G., Riggins, J.N., Harrington, M.G., 2006. Identification of disease markers in human cerebrospinal fluid using lipidomic and proteomic methods. Dis. Markers 22, 39–64.
Fridovich, I., 1986. Biological effects of the superoxide radical. Arch. Biochem. Biophys. 247, 1–11.
Gadad, B.S., Jha, M.K., Czysz, A., Furman, J.L., Mayes, T.L., Emslie, M.P., Trivedi, M.H., 2017. Peripheral biomarkers of major depression and antidepressant treatment response: current knowledge and future outlooks (In press). J. Affect. Disord.
Ghio, L., Gotelli, S., Cervetti, A., Respino, M., Natta, W., Marcenaro, M., Serafini, G., Vaggi, M., Amore, M., Belvederi Murri, M., 2015. Duration of untreated depression influences clinical outcomes and disability. J. Affect. Disord. 175, 224–228.
Goldsmith, D.R., Rapaport, M.H., Miller, B.J., 2016. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol. Psychiatry 21, 1696–1709.
Green, K.L., Brown, G.K., Jager-Hyman, S., Cha, J., Steer, R.A., Beck, A.T., 2015. The predictive validity of the beck depression inventory suicide item. J. Clin. Psychiatry 76, 1683–1686.
Grosso, G., Pajak, A., Marventano, S., Castellano, S., Galvano, F., Bucolo, C., Drago, F., Caraci, F., 2014. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. PLoS One 9, e96905.
Gururajan, A., Clarke, G., Dinan, T.G., Cryan, J.F., 2016. Molecular biomarkers of depression. Neurosci. Biobehav. Rev. 64, 101–133.
Haapakoski, R., Mathieu, J., Ebmeier, K.P., Alenius, H., Kivimaki, M., 2015. Cumulative meta-analysis of interleukins 6 and 1beta, tumour necrosis factor alpha and C-reactive protein in patients with major depressive disorder. Brain Behav. Immun. 49, 206–215.
Halaris, A., 2013. Inflammation, heart disease, and depression. Curr. Psychiatry Rep. 15, 400.
Halaris, A., 2017. Inflammation-associated co-morbidity between depression and cardiovascular disease. Curr. Top. Behav. Neurosci. 31, 45–70.
Halaris, A., Myint, A.M., Savant, V., Meresh, E., Lim, E., Guillemin, G., Hoppensteadt, D., Fareed, J., Sinacore, J., 2015. Does escitalopram reduce neurotoxicity in major depression? J. Psychiatr. Res. 66–67, 118–126.
Halliwell, B., 2006. Oxidative stress and neurodegeneration: where are we now? J. Neurochem. 97, 1634–1658.
Hayakawa, K., Kato, T.A., Kohjiro, M., Monji, A., Kanba, S., 2014. Minocycline, a microglial inhibitor, diminishes terminal patients' delirium? Am. J. Geriatr. Psychiatry 22, 314–315.
Herken, H., Gurel, A., Selek, S., Armutcu, F., Ozen, M.E., Bulut, M., Kap, O., Yumru, M., Savas, H.A., Akyol, O., 2007. Adenosine deaminase, nitric oxide, superoxide dismutase, and xanthine oxidase in patients with major depression: impact of antidepressant treatment. Arch. Med. Res. 38, 247–252.
Heron, D.S., Shinitzky, M., Hershkowitz, M., Samuel, D., 1980. Lipid fluidity markedly modulates the binding of serotonin to mouse brain membranes. Proc. Natl. Acad. Sci. USA 77, 7463–7467.
Horikawa, H., Kato, T.A., Mizoguchi, Y., Monji, A., Seki, Y., Ohkuri, T., Gotoh, L., Yonaha, M., Ueda, T., Hashioka, S., Kanba, S., 2010. Inhibitory effects of SSRIs on IFN-gamma induced microglial activation through the regulation of intracellular calcium. Prog. Neuropsychopharmacol. Biol. Psychiatry 34, 1306–1316.
Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med. 71, 171–186.
Kanchanatawan, B., Sirivichayakul, S., Ruxrungtham, K., Carvalho, A.F., Geffard, M., Ormstad, H., Anderson, G., Maes, M., 2017. Deficit, but not Nondeficit, schizophrenia is characterized by mucosa-associated activation of the tryptophan catabolite (TRYCAT) Pathway with highly specific increases in IgA responses directed to picolinic, xanthurenic, and quinolinic acid. Mol. Neurobiol.
Kato, T.A., Hashimoto, R., Hayakawa, K., Kubo, H., Watabe, M., Teo, A.R., Kanba, S., 2016. Multidimensional anatomy of 'modern type depression' in Japan: a proposal for a different diagnostic approach to depression beyond the DSM-5. Psychiatry Clin. Neurosci. 70, 7–23.
Kato, T.A., Kanba, S., 2017. Modern-Type Depression as an "Adjustment" Disorder in Japan: the Intersection of Collectivistic Society Encountering an Individualistic Performance-Based System. Am. J. Psychiatry 174, 1051–1053.
Kato, T.A., Monji, A., Mizoguchi, Y., Hashioka, S., Horikawa, H., Seki, Y., Kasai, M., Utsumi, H., Kanba, S., 2011a. Anti-Inflammatory properties of antipsychotics via microglia modulations: are antipsychotics a 'fire extinguisher' in the brain of schizophrenia? Mini Rev. Med. Chem. 11, 565–574.
Kato, T.A., Shinfuku, N., Fujisawa, D., Tateno, M., Ishida, T., Akiyama, T., Sartorius, N., Teo, A.R., Choi, T.Y., Wand, A.P., Balhara, Y.P., Chang, J.P., Chang, R.Y., Shadloo, B., Ahmed, H.U., Lerthattasilp, T., Umene-Nakano, W., Horikawa, H., Matsumoto, R., Kuga, H., Tanaka, M., Kanba, S., 2011b. Introducing the concept of modern depression in Japan; an international case vignette survey. J. Affect. Disord. 135, 66–76.
Kato, T.A., Shinfuku, N., Sartorius, N., Kanba, S., 2011c. Are Japan's hikikomori and depression in young people spreading abroad? Lancet 378, 1070.
Kato, T.A., Yamauchi, Y., Horikawa, H., Monji, A., Mizoguchi, Y., Seki, Y., Hayakawa, K., Utsumi, H., Kanba, S., 2013. Neurotransmitters, psychotropic drugs and microglia: clinical implications for psychiatry. Curr. Med. Chem. 20, 331–344.
Kunugi, H., Hori, H., Ogawa, S., 2015. Biochemical markers subtyping major depressive disorder. Psychiatry Clin. Neurosci. 69, 597–608.
Kupferberg, A., Bicks, L., Hasler, G., 2016. Social functioning in major depressive disorder. Neurosci. Biobehav. Rev. 69, 313–332.
Liu, T., Zhong, S., Liao, X., Chen, J., He, T., Lai, S., Jia, Y., 2015a. A meta-analysis of oxidative stress markers in depression. PLoS One 10, e0138904.
Liu, X., Zheng, P., Zhao, X., Zhang, Y., Hu, C., Li, J., Zhao, J., Zhou, J., Xie, P., Xu, G., 2015b. Discovery and validation of plasma biomarkers for major depressive disorder classification based on liquid chromatography-mass spectrometry. J. Proteome Res. 14, 2322–2330.
Liu, X., Li, J., Zheng, P., Zhao, X., Zhou, C., Hu, C., Hou, X., Wang, H., Xie, P., Xu, G., 2016. Plasma lipidomics reveals potential lipid markers of major depressive disorder. Anal. Bioanal. Chem. 408, 6497–6507.
Lucka, A., Arabska, J., Fife, E., Kroc, L., Soltysik, B.K., Kloszewska, I., Sobow, T., Kostka, T., Wysokinski, A., 2017. Atherogenic Indices Are Increased In Elderly Patients With Unipolar Depression-case-control Analysis. Metab. Syndr. Relat. Disord. 15, 291–295.
Lugo-Huitron, R., Blanco-Ayala, T., Ugalde-Muniz, P., Carrillo-Mora, P., Pedraza-Chaverri, J., Silva-Adaya, D., Maldonado, P.D., Torres, I., Pinzon, E., Ortiz-Islas, E., Lopez, T., Garcia, E., Pineda, B., Torres-Ramos, M., Santamaria, A., La Cruz, V.P., 2011. On the antioxidant properties of kynurenic acid: free radical scavenging activity and inhibition of oxidative stress. Neurotoxicol. Teratol. 33, 538–547.
Maes, M., Berk, M., Goehler, L., Song, C., Anderson, G., Galecki, P., Leonard, B., 2012. Depression and sickness behavior are Janus-faced responses to shared inflammatory pathways. BMC Med. 10, 66.
Maes, M., De Ruyter, M., Suy, E., 1986. Xanthurenic acid flow in 24-hour urine following L-tryptophan loading in depressive patients. Acta Psychiatr. Belg. 86, 120–130.
Maes, M., Delanghe, J., Meltzer, H.Y., Scharpe, S., D'Hondt, P., Cosyns, P., 1994. Lower degree of esterification of serum cholesterol in depression: relevance for depression and suicide research. Acta Psychiatr. Scand. 90, 252–258.
Maes, M., Galecki, P., Chang, Y.S., Berk, M., 2011a. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro)degenerative processes in that illness. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 676–692.
Maes, M., Leonard, B.E., Myint, A.M., Kubera, M., Verkerk, R., 2011b. The new '5-HT' hypothesis of depression: cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Prog. Neuropsychopharmacol. Biol. Psychiatry 35, 702–721.
Maes, M., Mihaylova, I., Kubera, M., Uytterhoeven, M., Vrydags, N., Bosmans, E., 2010. Increased plasma peroxides and serum oxidized low density lipoprotein antibodies in major depression: markers that further explain the higher incidence of neurodegeneration and coronary artery disease. J. Affect. Disord. 125, 287–294.
Maes, M., Mihaylova, I., Ruyter, M.D., Kubera, M., Bosmans, E., 2007. The immune effects of TRYCATs (tryptophan catabolites along the IDO pathway): relevance for depression - and other conditions characterized by tryptophan depletion induced by inflammation. Neuro Endocrinol. Lett. 28, 826–831.

Maes, M., Yirmyia, R., Noraberg, J., Brene, S., Hibbeln, J., Perini, G., Kubera, M., Bob, P., Lerer, B., Maj, M., 2009. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. Metab. Brain Dis. 24, 27–53.
Mann, J.J., Apter, A., Bertolote, J., Beautrais, A., Currier, D., Haas, A., Hegerl, U., Lonnqvist, J., Malone, K., Marusic, A., Mehlum, L., Patton, G., Phillips, M., Rutz, W., Rihmer, Z., Schmidtke, A., Shaffer, D., Silverman, M., Takahashi, Y., Varnik, A., Wasserman, D., Yip, P., Hendin, H., 2005. Suicide prevention strategies: a systematic review. JAMA 294, 2064–2074.
Martin-Subero, M., Anderson, G., Kanchanatawan, B., Berk, M., Maes, M., 2016. Comorbidity between depression and inflammatory bowel disease explained by immune-inflammatory, oxidative, and nitrosative stress; tryptophan catabolite; and gut-brain pathways. CNS Spectr. 21, 184–198.
Michel, T.M., Pulschen, D., Thome, J., 2012. The role of oxidative stress in depressive disorders. Curr. Pharm. Des. 18, 5890–5899.
Mitchell, A.J., Vaze, A., Rao, S., 2009. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet 374, 609–619.
Monji, A., Kato, T., Kanba, S., 2009. Cytokines and schizophrenia: microglia hypothesis of schizophrenia. Psychiatry Clin. Neurosci. 63, 257–265.
Muldoon, M.F., Manuck, S.B., Matthews, K.A., 1990. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. BMJ 301, 309–314.
Murakami, Y., Hoshi, M., Imamura, Y., Arioka, Y., Yamamoto, Y., Saito, K., 2013. Remarkable role of indoleamine 2,3-dioxygenase and tryptophan metabolites in infectious diseases: potential role in macrophage-mediated inflammatory diseases. Mediat. Inflamm. 2013, 391984.
Myint, A.M., 2012. Kynurenines: from the perspective of major psychiatric disorders. FEBS J. 279, 1375–1385.
Myint, A.M., Kim, Y.K., Verkerk, R., Scharpe, S., Steinbusch, H., Leonard, B., 2007. Kynurenine pathway in major depression: evidence of impaired neuroprotection. J. Affect. Disord. 98, 143–151.
Myint, A.M., Schwarz, M.J., Muller, N., 2012. The role of the kynurenine metabolism in major depression. J. Neural Transm. (Vienna) 119, 245–251.
Najjar, S., Pearlman, D.M., Devinsky, O., Najjar, A., Zagzag, D., 2013. Neurovascular unit dysfunction with blood-brain barrier hyperpermeability contributes to major depressive disorder: a review of clinical and experimental evidence. J. Neuroinflamm. 10, 142.
Nemeth, H., Toldi, J., Vecsei, L., 2005. Role of kynurenines in the central and peripheral nervous systems. Curr. Neurovasc. Res. 2, 249–260.
Ogawa, S., Fujii, T., Koga, N., Hori, H., Teraishi, T., Hattori, K., Noda, T., Higuchi, T., Motohashi, N., Kunugi, H., 2014. Plasma L-tryptophan concentration in major depressive disorder: new data and meta-analysis. J. Clin. Psychiatry 75, e906–e915.
Ohgidani, M., Kato, T.A., Haraguchi, Y., Matsushima, T., Mizoguchi, Y., Murakawa-Hirachi, T., Sagata, N., Monji, A., Kanba, S., 2016. Microglial CD206 gene has potential as a state marker of bipolar disorder. Front. Immunol. 7, 676.
Ormstad, H., Dahl, J., Verkerk, R., Andreassen, O.A., Maes, M., 2016. Increased plasma levels of competing amino acids, rather than lowered plasma tryptophan levels, are associated with a non-response to treatment in major depression. Eur. Neuropsychopharmacol. 26, 1286–1296.
Oxenkrug, G., 2013. Serotonin-kynurenine hypothesis of depression: historical overview and recent developments. Curr. Drug Targets 14, 514–521.
Parekh, A., Smeeth, D., Milner, Y., Thure, S., 2017. The role of lipid biomarkers in major depression. Healthcare 5 (Basel).
Parker, G., Brotchie, H., 2011. Mood effects of the amino acids tryptophan and tyrosine: 'food for Thought' III. Acta Psychiatr. Scand. 124, 417–426.
Peng, Y.F., Xiang, Y., Wei, Y.S., 2016. The significance of routine biochemical markers in patients with major depressive disorder. Sci. Rep. 6, 34402.
Price, L.H., Malison, R.T., McDougle, C.J., McCance-Katz, E.F., Owen, K.R., Heninger, G.R., 1997. Neurobiology of tryptophan depletion in depression: effects of m-chlorophenylpiperazine (mCPP). Neuropsychopharmacology 17, 342–350.
Roomruangwong, C., Kanchanatawan, B., Sirivichayakul, S., Anderson, G., Carvalho, A.F., Duleu, S., Geffard, M., Maes, M., 2017. IgM-mediated autoimmune responses to oxidative specific epitopes, but not nitrosylated adducts, are significantly decreased in pregnancy: association with bacterial translocation, perinatal and lifetime major depression and the tryptophan catabolite (TRYCAT) pathway. Metab. Brain Dis. 32, 1571–1583.
Rosenblat, J.D., Kakar, R., McIntyre, R.S., 2015. The cognitive effects of Antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int. J. Neuropsychopharmacol. 19.
Sato-Kasai, M., Kato, T.A., Ohgidani, M., Mizoguchi, Y., Sagata, N., Inamine, S., Horikawa, H., Hayakawa, K., Shimokawa, N., Kyuragi, S., Seki, Y., Monji, A., Kanba, S., 2016. Aripiprazole inhibits polyI: c-induced microglial activation possibly via TRPM7. Schizophr. Res. 178, 35–43.
Schrocksnadel, K., Wirleitner, B., Winkler, C., Fuchs, D., 2006. Monitoring tryptophan metabolism in chronic immune activation. Clin. Chim. Acta 364, 82–90.
Schwarcz, R., Bruno, J.P., Muchowski, P.J., Wu, H.Q., 2012. Kynurenines in the mammalian brain: when physiology meets pathology. Nat. Rev. Neurosci. 13, 465–477.
Schwarcz, R., Stone, T.W., 2017. The kynurenine pathway and the brain: challenges, controversies and promises. Neuropharmacology 112, 237–247.
Setoyama, D., Kato, T.A., Hashimoto, R., Kunugi, H., Hattori, K., Hayakawa, K., Sato-Kasai, M., Shimokawa, N., Kaneko, S., Yoshida, S., Goto, Y.I., Yasuda, Y., Yamamori, H., Ohgidani, M., Sagata, N., Miura, D., Kang, D., Kanba, S., 2016. Plasma metabolites predict severity of depression and suicidal ideation in psychiatric patients-a multicenter pilot analysis. PLoS One 11, e0165267.
Shelton, R.C., Miller, A.H., 2010. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. Prog. Neurobiol. 91, 275–299.
Shin, J.Y., Suls, J., Martin, R., 2008. Are cholesterol and depression inversely related? A meta-analysis of the association between two cardiac risk factors. Ann. Behav. Med. 36, 33–43.
Smith, K., 2014. Mental health: a world of depression. Nature 515, 181.
Sorci-Thomas, M.G., Thomas, M.J., 2016. Microdomains, inflammation, and atherosclerosis. Circ. Res. 118, 679–691.
Steiner, J., Walter, M., Gos, T., Guillemin, G.J., Bernstein, H.G., Sarnyai, Z., Mawrin, C., Brisch, R., Bielau, H., Meyer zu Schwabedissen, L., Bogerts, B., Myint, A.M., 2011. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? J. Neuroinflamm. 8, 94.
Sublette, M.E., Galfalvy, H.C., Fuchs, D., Lapidus, M., Grunebaum, M.F., Oquendo, M.A., Mann, J.J., Postolache, T.T., 2011. Plasma kynurenine levels are elevated in suicide attempters with major depressive disorder. Brain Behav. Immun. 25, 1272–1278.
Tosi, M.R., Tugnoli, V., 2005. Cholesteryl esters in malignancy. Clin. Chim. Acta 359, 27–45.
Weng, R., Shen, S., Burton, C., Yang, L., Nie, H., Tian, Y., Bai, Y., Liu, H., 2016. Lipidomic profiling of tryptophan hydroxylase 2 knockout mice reveals novel lipid biomarkers associated with serotonin deficiency. Anal. Bioanal. Chem. 408, 2963–2973.
Wu, S., Ding, Y., Wu, F., Xie, G., Hou, J., Mao, P., 2016. Serum lipid levels and suicidality: a meta-analysis of 65 epidemiological studies. J. Psychiatry Neurosci. 41, 56–69.
Xu, H.B., Fang, L., Hu, Z.C., Chen, Y.C., Chen, J.J., Li, F.F., Lu, J., Mu, J., Xie, P., 2012. Potential clinical utility of plasma amino acid profiling in the detection of major depressive disorder. Psychiatry Res. 200, 1054–1057.
Yatham, L.N., Liddle, P.F., Sossi, V., Erez, J., Vafai, N., Lam, R.W., Blinder, S., 2012. Positron emission tomography study of the effects of tryptophan depletion on brain serotonin(2) receptors in subjects recently remitted from major depression. Arch. Gen. Psychiatry 69, 601–609.
Young, S.N., 2013. Acute tryptophan depletion in humans: a review of theoretical, practical and ethical aspects. J. Psychiatry Neurosci. 38, 294–305.
Young, S.N., Smith, S.E., Pihl, R.O., Ervin, F.R., 1985. Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology (Berl.) 87, 173–177.
Zinellu, A., Sotgia, S., Mangoni, A.A., Sanna, M., Satta, A.E., Carru, C., 2015. Impact of cholesterol lowering treatment on plasma kynurenine and tryptophan concentrations in chronic kidney disease: relationship with oxidative stress improvement. Nutr. Metab. Cardiovasc. Dis. 25, 153–159.