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Indoleamine 2,3-dioxygenase and Immune Changes Under Antidepressive Treatment in Major Depression in Females

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Abstract. *Background/Aim: Indoleamine 2, 3-dioxygenase (IDO) induction has been suggested as a mechanism by which immune activation affects tryptophan metabolism and serotonin synthesis in major depressive disorder (MDD). We investigated IDO and changes in inflammatory mediators in patients with MDD undergoing effective treatment. Patients and Methods: Forty female patients with MDD and 40 controls were recruited. Serum IDO was assessed by enzyme-linked immunosorbent assay (ELISA). We also determined tumor necrosis factor-α (TNFα), interferon-γ (IFNγ), C-reactive protein (CRP) and serotonin concentrations. Results: Patients' baseline concentrations of IDO and immune mediators were higher and serotonin concentrations were lower compared to controls. IDO and TNFα concentrations decreased under treatment and IDO changes were positively correlated with patient improvement. IFNγ and CRP concentrations remained unchanged. Serotonin concentration tended to increase. Conclusion: IDO might play an important role in the pathophysiology of MDD. Moreover, antidepressant therapy might reduce IDO production through an IFNγ-independent pathway. Finally, peripheral concentration of IDO assessed by ELISA might be a useful marker of MDD.*

There are mounting data suggesting that inflammation may be a pivotal pathway to major depressive disorder (MDD) (1-3). Peripheral blood elevation of pro-inflammatory cytokines and the acute-phase reactant C-reactive protein (CRP) are some of the most reliable biomarkers of inflammation in MDD (4-6).

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Moreover, administrations of innate immune cytokines or agents, such as lipopolysaccharide or typhoid vaccination, which stimulate an innate immune response induce depressive-like behaviors in both animals and humans (7, 8).

Immune mediators access the brain, interact with many pathophysiological domains relevant to depression and affect the synthesis, release and re-uptake of neurotransmitters (9, 10). The synthesis and release of brain serotonin depends on the availability of tryptophan in blood and brain (11). An association between the immune system and tryptophan metabolism through the kynurenine pathway (KP) in the pathophysiology of MDD is suggested by the finding that KP is involved in both immune activation and neurochemical-cellular abnormalities in the brain (12, 13). Tryptophan is the precursor of serotonin, melatonin and kynurenine. The rate-limiting enzymes in initialization of the KP are tryptophan dioxygenase (TDO) in the liver and IDO in the placenta, lungs, blood and brain (14). TDO metabolizes tryptophan exclusively (15), whereas IDO also metabolizes serotonin and melatonin (16). Kynurenine is catabolized into downstream neuroactive metabolites through the KP. The further conversion of kynurenine to either kynurenic acid (neuroprotective) or 3-hydroxykynurenine, the precursor of quinolinic acid (neurodegenerative), is mediated by the enzymes kynurenine aminotransferase and kynurenine monooxygenase. Quinolinic acid is catabolized into nimotinamide adenine dinucleotide (NAD) (17). In the brain, tryptophan is catabolized in the microglia and astrocytes, although 60% of brain kynurenine is produced in the periphery (18). Increased quinolinic acid is strongly associated with depressive symptoms (19). The activities of IDO and kynurenine monooxygenase are strongly regulated by cytokines, although TDO activity is not. Pro-inflammatory cytokines such as interferon-γ (IFNγ), interferon-α (IFNα), and tumor necrosis factor-α (TNFα) are potent inducers of IDO through stimulation of multiple inflammatory signaling pathways, whereas anti-inflammatory cytokines may act as

IDO inhibitors (20-22). Moreover, activation of IDO has been noted in patients undergoing IFN-α therapy for hepatitis C who subsequently developed MDD (23). Thus, IDO induction might participate in the mechanism by which the inflammatory response system is implicated in MDD *via* tryptophan metabolism.

Extensive clinical studies have assessed IDO activity in MDD indirectly by the kynurenine: tryptophan ratio (24-30) or by IDO gene expression (25). Most were cross-sectional, with the exception of a study assessing IDO activity changes under anti-depressant drug treatment (28). Additionally, most studies did not concurrently investigate inflammatory mediators which affect IDO synthesis (31) and activity. The aim of the present study was the concurrent investigation of serum changes in IDO and levels of inflammatory mediators in MDD and their association with serotonin synthesis through tryptophan metabolism under successful antidepressive treatment.

Materials and Methods

Patients. Forty female patients (mean age=51.1±10.7 years) with a diagnosis of MDD and 40 female healthy controls participated in the study. The controls were matched with the patients with respect to age, body mass index (BMI) and menopausal status. Both patients and controls gave their informed consent and the protocol of the study was approved by the local Ethics Committee. The study was carried out in the Women's Inpatient Unit of our hospital, which explains the exclusively female composition of the sample. Criteria for participation in the study were: a diagnosis of a major depressive episode in the context of MDD according to DSM-IV-TR-criteria (32). Candidate participants in the study with chronic illnesses known to affect the immune status, or acute infections, allergic reactions, internal or neurological disorders were excluded. Diagnostic assessment of both patients and controls was confirmed through the administration of the Structured Clinical Interview for the diagnosis of DSM-IV (33). On admission, patients were also rated on the Hamilton Depression Rating Scale (HDRS). Twenty patients had proved resistant to antidepressant treatment during their index episode, and were referred for electroconvulsive therapy (ECT). All patients were drug-free for at least one week prior to admission, with the exception of those treated with low-dose benzodiazepines (up to the equivalent to 5 mg of diazepam daily). Twenty patients underwent pharmacological treatment of six weeks' duration with first-line antidepressants at adequate dosages, mainly with selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors or a combination of both. All had remitted by the end of the sixth week (reduction of their HDRS score ≥50%) and were discharged from hospital. Patients in the ECT group underwent a series of 8-12 bilateral ECT sessions. All patients remitted after ECT and were discharged from hospital two days after their last ECT session.

Blood sampling. All participants having fasted from midnight presented for blood sampling early in the morning. Peripheral blood was collected from all patients and controls into serum separator tubes. Baseline blood samples in patients with MDD were collected on admission, and final blood samples before discharge from hospital (pharmacotherapy patients) or 24 hours after the last ECT session (ECT group). Blood samples were immediately centrifuged and serum samples were aliquoted and stored at −80˚C until analysis.

Serum TNFα, IFNγ, CRP, serotonin and IDO measurements. Serum TNFα, IFNγ, Serotonin and IDO were determined by enzyme-linked immunosorbent assay (ELISA). Serum concentrations of TNFα and IFNγ were determined using Quantikine Human TNF-α, and IFN-γ ELISA kits (R&D Systems, UK, Supplied by Anti-cell, Athens, Greece). These assays employ the quantitative sandwich enzyme immunoassay technique. The assays' mean minimum detectable levels were 1.6 pg/ml for TNFα, and typically less than 8 pg/ml for IFNγ.

Serum serotonin levels were determined using Serotonin Elisa Kit (IBL International GMBH, Supplied by Anti-cell, Athens, Greece). Sample preparation (derivatization of serotonin to N-acylserotonin) was achieved by acylation of samples with overnight incubation, according to the manufacturer's instructions (long version of acylation of samples). The assay procedure follows the basic principle of competitive ELISA. The assay's lower detection limit for serum serotonin was 1.50 ng/ml (overnight version).

Serum IDO concentrations were measured using Human Indoleamine 2, 3-doxygenase ELISA Kit (Cusabio Biotech Co. Ltd., Supplied by Anti-cell, Athens, Greece).This assay employs the quantitative sandwich enzyme immunoassay technique. The minimum detectable level of human IDO was typically less than 0.195 ng/ml. These immunoassays were performed according to manufacturer's instructions.

Finally, serum CRP concentrations were determined by means of particle enhanced highly sensitive immunonephelometry using Cardio Phase hs CRP (high sensitive C-reactive protein) and analyses were carried out on BN// Behring Nephelometer II system (Supplied by Siemens Healthcare Diagnostics, Athens, Greece). A typical detection limit for CRP was 0.0175 mg/dl.

Statistical analysis. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc, Chicago IL, USA) and Stata statistical software package version 11.0 (StataCorp LP, College Station, TX, USA). Logarithmic transformation was used to improve normality of distribution for biochemical variables when required. Student's *t*-tests for independent and for paired samples were used to compare mean (or mean log-transformed) values of patients with MDD *vs*. controls and of final *vs*. baseline values of patients, respectively; when normality in distribution remained unsatisfactory, even after logarithmic transformation, the non-parametric Wilcoxon–Mann–Whitney test (for independent samples) and Wilcoxon signed-rank test (for paired samples) were used instead. Multiple linear regression models were utilized to examine possible confounding effects of age and BMI on biochemical results, *a priori* adjusting for these two parameters. Bivariate correlations between parameters were examined using Spearman's correlation coefficient. A cut-off point of p-value <0.05 was used to mark statistical significance.

Results

The mean HDRS score for patients on admission was 35.7±7.62 and 15.7±8.99 before discharge from Hospital (p<0.001). Patients' baseline BMI did not differ significantly from that of controls. At baseline, mean serum concentrations of IDO, TNFα, IFNγ and CRP were significantly higher in patients than controls (p<0.001), while the mean serotonin concentration was significantly lower (p<0.001) (Table I).

Table I. *Comparisons between study participants according to depression status*.

Parameter		Patients		*p*-Value		
	Controls (N=40)	Baseline	Final	Baseline *vs*. controls	Final *vs*. controls	Final *vs*. baseline
Age (years)	52.3 (8.44)	51.1 (10.7)	-	0.579	-	-
Menopause	17 (42.5%)	19 (47.5%)	-	0.822	-	-
BMI (kg/m2)	26.4 (3.40)	26.6 (5.80)	26.7 (6.00)	0.845	0.824	0.003
HDRS	-	35.7 (7.62)	15.7 (8.99)	-	-	<0.001
CRP^{LN} (mg/dl)	0.07 (0.033)	0.46 (0.587)	0.39 (0.582)	<0.001[aa]	<0.001[aa]	0.145
$TNF\alpha^{LN}$ (pg/ml)	4.55 (1.841)	7.35 (1.972)	6.94 (2.116)	<0.001[aa]	0.001[aa]	0.041
$IFN\gamma^{NP}$ (pg/ml)	10.85 (0.189)	11.12 (0.991)	11.32 (0.696)	<0.001[a]	<0.001[aa]	0.352
IDO^{LN} (ng/ml)	4.14 (4.266)	16.79 (13.534)	12.41 (10.960)	<0.001[aa]	<0.001[aa]	<0.001
$Serotonin^{NP}$ (ng/ml)	197.39 (122.549)	20.86 (7.949)	24.62 (25.930)	<0.001[aa]	<0.001[aa]	0.156

Data are mean±SD, or number (%). a superscripts: comparisons between (all) patients with Major Depressive Disorder vs. controls, when adjusting for age and BMI in multiple regression; [a]*p*-value <0.05; [aa]*p*-value <0.01. LN: original mean values shown in table, but log-transformed variables used for statistical analysis due to skewness. NP: non-parametric tests used due to lack of normality. BMI: Body Mass Index; HDRS: Hamilton Depression Rating Scale; CRP: C - Reactive Protein; TNFa: Tumor Necrosis Factor - α; IFNγ: Interferon - γ; IDO: indoleamine 2,3-dioxygenase.

Table II. *Correlations of sample parameters at baseline*.

Parameters (baseline)		HDRS*	CRP	TNFα	IFNγ	IDO
CRP (mg/dl)	Rho	–0.171	–	–	–	–
	p-Value	0.303	–	–	–	–
TNFa (pg/ml)	Rho	0.204	0.559	–	–	–
	p-Value	0.219	<0.001[h]	–	–	–
IFNγ (pg/ml)	Rho	–0.108	0.521	0.551	–	–
	p-Value	0.517	<0.001[a]	<0.001[b]	–	–
IDO (ng/ml)	Rho	–0.125	0.481	0.391	0.434	–
	p-Value	0.462	<0.001[c]	<0.001	0.001	–
Serotonin (ng/ml)	Rho	0.005	–0.469	–0.586	–0.551	–0.529
	p-Value	0.977	<0.001	<0.001	<0.001	<0.001

*Correlations examined in patients only; all other correlations refer to whole study sample (patients and controls together). Correlation significant: [a]in controls when examined separately (*p*-value <0.05); [b]in patients when examined separately (*p*-value <0.05). HDRS: Hamilton Depression Rating Scale; CRP: C - Reactive Protein; TNFa: Tumor Necrosis Factor - α; IFNγ: Interferon-γ; IDO: indoleamine 2,3-dioxygenase.

Baseline IDO was positively correlated with IFNγ (Rho=0.434, $p<0.001$), and TNFα (Rho=0.391, $p<0.001$) in both patients and controls, and with CRP in controls (Rho=0.481, $p<0.001$). Serotonin was negatively correlated with IDO (Rho=–0.529, $p<0.001$), IFNγ (Rho=–0.551, $p<0.001$), TNFα (Rho=–0.586, $p<0.001$) and CRP (Rho=–0.469, $p<0.001$) in both patients and controls. CRP was positively correlated with TNFα (Rho=0.559, $p<0.001$) in patients. Moreover, IFNγ was positively correlated with TNFα (Rho=0.551, $p<0.001$) in patients and with CRP (Rho=0.521, $p<0.001$) in controls (see Table II).

Post-treatment IDO and TNFα concentrations decreased significantly ($p<0.001$ and $p<0.05$ respectively), whereas IFNγ concentrations did not change, and CRP concentrations showed a modest decrease. Serotonin concentrations increased under treatment by 18%, although this change did not reach statistical significance. Although post-treatment IDO, TNFα and CRP concentrations decreased, they were still elevated compared to controls. Treatment changes in IDO levels co-varied with change in patients' HDRS scores (Rho 0.342, $p<0.038$).

Discussion

We comparatively assessed serum concentrations of IDO and inflammatory mediators and their association with serotonin synthesis in 40 female patients with MDD and 40 matched controls, as well as their changes under successful anti-depressive treatment. As expected, we found that circulating pro-inflammatory cytokines TNFα and IFNγ and CRP were significantly increased in patients relative to controls (6, 34, 35). Moreover, TNFα was positively correlated with IFNγ and CRP in patients. Of note, for CRP we used a high sensitivity

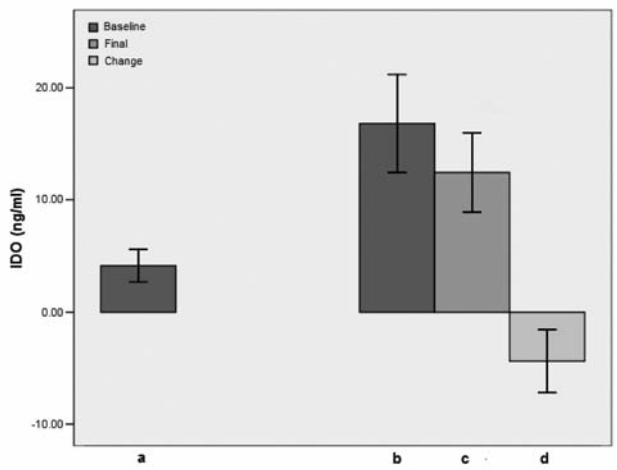

Figure 1. *Indoleamine 2,3-dioxygenase (mean, 95% Confidence Interval) by depression status. a: Healthy controls; b: patients with Major Depressive Disorder at baseline; c: patients with Major Depressive Disorder post-treatment; d: Indoleamine 2,3-dioxygenase change of patients under treatment.*

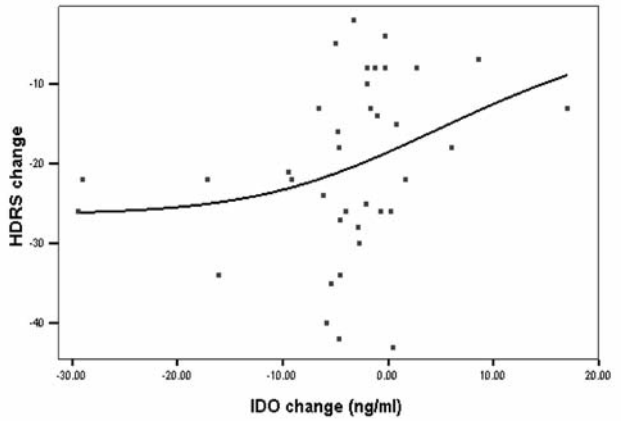

Figure 2. *Hamilton Depression Rating Scale and Indoleamine 2,3-dioxygenase (plus smoothing line) in patients with Major Depressive Disorder under treatment.*

assay since it is a more sensitive marker of inflammation, having a range of measurement that extends below that typical of most conventional assays. In addition patients' serotonin concentrations were significantly lower than the controls' and serotonin was negatively correlated with IDO and all inflammatory mediators.

Serum IDO concentrations were significantly increased in patients compared to controls. There is only one cross-sectional study assessing plasma IDO concentrations by ELISA assay in patients suffering from pain and depression, which found that the kynurenine:tryptophan ratio co-varied with plasma IDO concentrations (26). This finding agrees with those of other studies assessing IDO activity indirectly by the kynurenine:tryptophan ratio (24, 26-30), which found enhanced IDO activity in patients with MDD compared to controls.

We also found a strong positive correlation between IDO and IFNγ. IDO protein is encoded by the *IDO1* and *IDO2* genes. IDO1 gene transcription is strongly controlled by specific inflammatory mediators. The human IDO gene promoters contain multiple sequence elements that confer responsiveness to type I (IFNα and -β) and type II (IFNγ) interferons (14, 31). Signal transducer and activator of transcription 1 (STAT1) and IFN-regulatory factor 1 function synergistically to mediate the induction of IDO expression by IFNγ (36). Furthermore, we found a strong positive association between IDO and TNFα. This is supported by other studies suggesting that TNFα may act cooperatively with IFNγ to enhance IDO expression *in vitro* (37).

However, such enhanced IDO production and activity by inflammatory mediators might function as an immunoregulatory mechanism by suppressing T-cell response and by affecting lymphocyte proliferation (14). Moreover, another study suggested that IDO induction in IFNγ-activated astroglia and subsequent *de novo* NAD synthesis, through tryptophan metabolism, might maintain intracellular NAD levels and cell viability under conditions of oxidative stress (38). Our results suggest that elevated serum IDO concentrations might regulate the increased production of inflammatory mediators and also maintain cell viability by increasing concentrations of oxidative metabolites in MDD.

These findings, along with that of a strong negative correlation between IDO and serotonin, support the hypothesis that increased pro-inflammatory cytokines TNFα and IFNγ induce the production of IDO in MDD, resulting in an imbalance in tryptophan metabolism with activation of the KP and reduced serotonin synthesis. IDO induction also leads to further serotonin degradation into formyl-5-hydroxykynuramine (39), resulting in deficient serotonergic neurotransmission. Our findings are in agreement with another study which found enhanced IDO activity, as assessed by kynurenine:tryptophan ratio, and decreased plasma concentrations of kynurenic acid in patients with MDD compared to controls (28). The authors suggested that tryptophan was metabolized down the neurotoxic arm of the KP, thus leading to reduced serotonin synthesis (28). However, other authors investigating *IDO1* and *IDO2* gene expression in MDD suggested that tryptophan depletion in patients is not mediated by activation of the KP (25). Activation of IDO was found in patients undergoing IFNα therapy for hepatitis C who developed depression (23, 40). It has also been suggested that depressive symptoms following cytokine-induced IDO activity may also result from elevated production of metabolites of the KP (22, 41).

Another novel finding of our study was that post-treatment serum concentrations of IDO were significantly decreased compared to baseline, though they were still elevated compared to controls (Figure 1). The reduction of IDO levels might be the result of the moderation of the inflammatory mediators, that enhanced its production, by antidepressive treatment, which has been proved to have anti-inflammatory effects (42). Although Myint and colleagues found that the kynurenine:tryptophan ratio tended to increase after antidepressant treatment in patients with MDD, they acknowledged that this was not due to over-production of kynurenine induced by IDO activity but to the reduction of further metabolism of kynurenine by anti-inflammatory effects of antidepressants on cytokines, which would otherwise also enhance the activity of IDO and kynurenine monooxygenase (28). Our finding that serum IDO changes correlated with HDRS changes in patients with MDD suggests that IDO decrease is a component of the therapeutic process, despite an only modest increase of serum serotonin concentrations (Figure 2). There are studies suggesting that the remission of depressive symptoms might also be the result of the reduction of the neurodegenerative –neurotoxic metabolite production, as a consequence of IDO decrease after treatment.

Given that IFNγ concentrations remained unchanged by treatment, we could hypothesize that antidepressant therapy affects IDO indirectly, possibly by an IFNγ-independent pathway, resulting in decreased serum concentrations of IDO. This alternative pathway might be modulated by additional signaling pathways and cytokines produced by specific cell types such as fibroblasts (43). Fujigaki and colleagues found IDO induction, by lipopolysaccharide in blood mononuclear cells through p38 mitogen-activated protein kinase and nuclear factor-ϰB pathways, along with the synergistic effect of proinflammatory cytokines (21). This suggests that transcriptional and post-translational IDO regulation are complex and cell type-specific. Moreover, certain proinflammatory signals might down-regulate IDO expression by cells that would normally express it, such as dendritic cells (44).

Among the limitations of the present study, we should stress that we did not measure the kynurenine:tryptophan ratio in order to confirm its reported co-variation with serum IDO levels (26), as well as several key components of the inflammatory mechanism underlying MDD. Moreover, we did not investigate possible differential changes under different treatment modalities, namely antidepressant medication and ECT.

Despite these limitations, our findings strongly suggest that IDO plays an important role in the pathophysiology of MDD, and that effective antidepressant treatments of various modalities are associated with decreased IDO production through an IFNγ-independent pathway. Finally, peripheral IDO concentrations assessed by ELISA might be a useful marker of MDD.

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