Psychiatric Illness in Dialysis Patients : Depression and Its Effects on Nutritional Status in Chronic Hemodialysis Patients

한림대학교 의과대학 춘천성심병원 신장내과, 정신과*

구자룡 · 이상규* · 손봉기*

Depression is generally accepted to be the most common psychological complication of chronic dialysis patients[1, 2]. Although the reported incidence of depression in patients with maintenance dialysis varies widely, these differences are based in part upon the different criteria and methodology utilized to diagnose depression[2, 3]. Depression has been demonstrated to predict mortality in a variety of medical condition[4, 5]. The studies on maintenance dialysis patients also showed a significant association of depression with mortality[6-8]. However the causal relation between depression and increased mortality is uncertain.

It is well known that chronic hemodialysis (HD) patients with malnutrition, as manifested in part by hypoalbuminemia, have an increased mortality rate[9]. Depression is commonly associated with poor oral intake which can aggravate malnutrition of chronic HD patients. Recent studies also showed the positive relation between depression and pro-inflammatory cytokines[10, 11]. Increased cytokine and inflammatory response in end-stage renal disease (ESRD) patients can cause malnutrition by increased protein catabolism, which contribute to increased mortality in ESRD patients[12]. In view of these considerations, we hypothesized that depression in maintenance HD patients may have important interactions with malnutrition. We undertook a cross-sectional study to investigate the relation between the nutritional status and depression in chronic HD patients. Then the effect of anti-depression treatment on nutritional status was evaluated in selected patients.

본 연제의 내용은 저자들에 의해 American Journal of Kidney Diseases (41:1037-1041, 2003)와 The American Journal of the Medical Sciences (in press, 2004)에 발표 및 발표예정인 상태이며 본 강연을 위하여 그 내용을 발췌 정리하였음.

Methods

1. Cross-sectional study

This study enrolled 76 chronic renal failure patients who dialyzed for more than 6 months at the outpatients HD unit of Hallym university hospital (Chunchon, Korea). All were free of acute illness within the past three months, and none were receiving corticosteroids. Among those patients, 14 patients who were uncooperative to this study or refused to answer depression scale inventory were excluded. Sixty-two patients completed the cross-sectional study. The cause of chronic renal failure was diabetic nephropathy in 18 patients (29.0%), hypertension in 14 patients (22.6%), chronic glomerulonephritis in 8 patients (12.9%), polycystic kidney disease in 3 patients (4.8%), unknown and miscellaneous in the remainder. The patients received three 4-4.5 hours sessions of HD per week using bicarbonate-buffered dialysate. The dialysis membrane used in all these patients was composed of modified cellulose (Hemophane) with a surface area of 1.1 m^2. For-

ty-nine patients received recombinant human erythropoietin and most patients were on antihypertensive medication (ACE inhibitor, calcium-channel blockers, alpha and beta-blockers, vasodilator) as well as other drugs commonly used in chronic HD such as phosphate- and potassium-binders, and vitamin B, C, and D supplements. None of included patients received tricyclic antidepressant.

1) Measure of depression

All patients were administered a Beck Depression Inventory (BDI) questionnaire[13]. The BDI is a 21 item self-report rating inventory measuring characteristic attitudes and symptoms of depression. The 21 items are answered on a 4-point Likert scale that represents 0 as the absence of a problem, and 3 as an extreme problem, with a total score range of 0 to 63 (5-9, normal; 10-18, mild to moderate depression; 19-29, moderate to severe depression; 30-63, severe depression). The BDI is a well-validated index of depression and correlates well with diagnostic criteria[14]. The advantage of the BDI is that it places the subject within a range of depression severity, rather than merely identifying if the person meets diagnostic criteria. It has been used frequently to assess depression in patients with ESRD[1, 7, 15] and is a useful screen for potentially treatable clinical depression in ESRD population[2]. It is reported that 85% of Western dialysis patients with BDI scores of 11 or greater met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) criteria for the diagnosis of major depression[2] and BDI scores predicted mortality in HD patients[7]. The mean BDI score of normal Korean population was reported as 12.7 ± 7.7 which is significantly higher than that of the western population[16]. The BDI score of 21 has been also suggested as a cut-off value for the diagnosis of depression for Korean population[16].

2) Assessment of nutritional status

Modified subjective global assessment (SGA) used in the Canada-USA Peritoneal Dialysis Study[17] was used to evaluate the overall protein-energy nutritional status. The SGA included four items (weight loss over past six months, anorexia, subcutaneous fat, and muscle mass) scored on a seven-point Likert scale. Scores of 1-2 represented severe malnutrition, 3-5 moderate to mild malnutrition, and 6-7 normal nutrition. The SGA scores were determined by a clinician who was not an investigator. For anthropometric measurements, body mass index (BMI), defined as the dry weight in kilograms divided by the square of the height in meters and triceps skinfold thickness (TSF) in the fistula-free arm using Harpenden caliper (British Indicators Ltd., West Sussex, UK) were measured. Each TSF measurement was repeated three times and the median value was recorded. The mid-arm muscle circumference (MAMC) was derived from TSF and mid-arm circumference (MAC) as follows : $MAMC = MAC - (\Pi \times TSF)$[18].

3) Dialysis adequacy and biochemical analyses

Dialysis adequacy (KT/V_{urea} : K, dialyzer urea clearance, mL/minute; T, HD session length, minute; V, volume of distribution of urea, mL) and normalized protein catabolic rate (nPCR) as a marker of protein intake were calculated by variable volume, single pool urea kinetic calculator on web site (HDCN, Hypertension Dialysis Clinical Nephrology, http://www.hdcn.com/)[19]. The contribution of residual renal function was included in the calculation. Plasma intact parathyroid hormone (PTH) levels were measured with specific radioimmunoassays. Urea, albumin, hematocrit and bicarbonate were measured by standard techniques. Samples were non-fasting and collected immediately after initiation of HD.

Of 40 patients who had BDI score greater than 18, 34 patients met DSM-IV criteria for major depressive disorder. This means that 54.8% (34/62) of the prevalent population studied had de-

pression. Thirty-four of 35 patients with BDI score greater than 21, which is the cut-off score for the diagnosis of depression for Korean population16, met the DSM-IV criteria for major depressive disorder.

2. Longitudinal study

Among sixty-two patients who completed the cross-sectional study, 34 patients who had score greater than 18 on the BDI score and met DSM-IV criteria for major depressive disorder were assigned to the treatment group and received selective serotonin reuptake inhibitors paroxetine 10 mg/day and supportive psychotherapy conducted by independent psychiatrist for a total of 8 weeks of treatment. Remaining 28 patients were assigned to the control group who received neither medication nor psychotherapy. During the course of this study, dry weight, HD session length and dialyzer were not changed. The study protocol was approved by the Hallym University Hospital Institutional Review Board, and all patients gave informed consent.

1) Measure of depression

In the treatment group, change in the severity of depression before and after depression treatment was ascertained by administering the Hamilton Depression Rating Scale (HDRS) and Zung Self Rating Depression Scale (SDS). In the longitudinal study, we did not use BDI because some patients were reluctant to fill up repeatedly same BDI questionnaire administered in previous cross-sectional study.

HDRS is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and co-morbid anxiety symptoms [20]. It provides ratings on current DSM-IV symptoms of depression, with the exceptions of hypersomnia, increased appetite, and concentration/indecision.

The 17-items are rated on either a 5-point (0-4) or a 3-point (0-2) scale. In general, the 5-point scale items use a rating of 0, absent; 1, doubtful to mild; 2, mild to moderate; 3, moderate to severe; 4, very severe. A rating of 4 is usually reserved for extreme symptoms. The 3-point scale items used a rating of 0, absent; 1, probable or mild; 2, definite. Total score range from 0 to 53 with normal (0-6), mild (7-17), moderate (18-24) and severe (25-53) depression. A psychiatrist who was not an investigator determined the HDRS scores.

SDS is a 20 question self-rating assessment for depression which is much simpler than BDI questionnaire[21]. The 20 items are answered on a 4-point Likert scale that represents 1 as minimal (none or little of time) and 4 as severe (most or all of the time) problem and raw score is converted to 100 point scale with a total score range of 35 to 100 (35-49, normal; 50-59, mild depression; 60-69, moderate depression; 70-100, severe depression).

2) Multi-frequency segmental bioimpedance analysis (BIA)

It is possible by multi-frequency BIA, to distinguish total body water (TBW) and extracellular fluid (ECF) by using the resistance of cell membranes to relatively low frequency currents[22]. At high frequencies, currents flow across both intra- and extracellular spaces, but at low frequencies, currents flow mainly through extracellular space, allowing the assessment of ECF alone. Segmental BIA can measure the resistance of the trunk or each limb separately. The results of segmental BIA of the trunk and extremity are then summed up to produce whole body BIA. It is a more appropriate approach to monitor body water during HD than whole body BIA, because changes in local resistance can be allocated to segments with uniform geometry and resistivity [23]. Water volumes are calculated by means of population based regression equation using impedance index (height^2/resistance). Lean body mass that contains 73.4% of TBW is determined and

fat mass can be calculated by subtracting lean body mass from body weight.

Eight stainless tactile electrodes were used to measure the impedance of the trunk and extremity (Inbody 2.0, Biospace Co, Ltd., Seoul, Korea) as used in other study[24]. The hand electrode consisted of thumb pipe and palm cylinder electrodes, and the foot electrode consisted of frontal and rear sole plate electrodes. Impedance was measured at frequencies of 5, 50, 250, and 500 kHz. The validation of the method has been reported using a sodium bromide dilution and a deuterium oxide dilution[22]. The water volume in trunk measured by BIA was compared with water volume measured by dual energy X-ray absorptiometry (DEXA) as the reference in 171 healthy subjects, giving correlation coefficient of 0.982 and standard error of estimation of 0.695L. The measurements were performed at 30 min after HD in standing position. BIA was done repeatedly before and after anti-depression treatment.

3) Markers of nutritional status, dialysis adequacy and biochemical analyses

SGA and BMI, dialysis adequacy, nPCR and other biochemical markers were measured before and after anti-depression treatment as described in cross-sectional study.

3. Statistical analysis

Data analysis was performed using a statistical software program (SPSS for windows 9.0). Data are presented as mean±SD. Correlations between the degree of depression and age and various nutritional parameters were assessed using Pearson's correlations coefficients. Differences between groups were assessed by unpaired Student's *t*-test and chi-square test. To compare values obtained at baseline and 8 weeks of treatment, paired t-test was used. P values less than 0.05 were considered significant.

Results

1. Cross-sectional study

The principal clinical data and nutritional status of patients are presented in Table 1. The mean total BDI score was 22.7±11, which falls in the range of moderate to severe depression by the criteria for western population. The distribution of BDI score according to the severity of depression is shown in Table 2. Thirty-five (56.5 %) patients had BDI score greater than 21 which is the cut-off score for the diagnosis of depression for Korean population. There was a significant correlation between the age and BDI score ($r=0.45$, $p<0.001$). Diabetic patients had signifi-

Table 1. Clinical Characteristics and Nutritional Parameters (N=62)

Age (year)	48.8±11.1
Male (%)	56.5
Hemodialysis duration (month)	51.9±32.7
Diabetes mellitus (%)	29
KT/Vurea	1.28±0.20
Hematocrit (%)	25.9±4.8
Plasma bicarbonate (meq/L)	17.9±3.2
Plasma intact PTH (pg/mL)	114.1±100.9
Serum albumin (g/dL)	3.96±0.46
nPCR (g/kg/day)	1.13±0.24
Subjective global assessment	4.4±1.8
Anthropometry	
Triceps skinfold thickness (mm)	9.7±4.0
Midarm muscle circumference (cm)	21.5±2.1
Body mass index (kg/m^2)	
Male	20.9±2.8
Female	20.5±3.2

Values are expressed as mean±SD unless otherwise noted

Table 2. Distribution of the BDI Scores

Levels of depression	BDI Score	N (%)
Normal	5-9	8 (12.9)
Mild to moderate	10-18	14 (22.6)
Moderate to severe	19-29	24 (38.7)
Severe	30-63	16 (25.8)

cantly higher BDI score than non-diabetic patients (29.7±9.7 versus 19.8±10.9, p<0.001). The BDI score was negatively correlated with various nutritional parameters (Table 3). There was no significant correlation between the BDI score and duration of maintenance HD, KT/V_{urea}, dose of erythropoietin, hematocrit, blood urea nitrogen (BUN), plasma bicarbonate and intact PTH concentration (data are not shown).

Table 3. Correlations between the BDI Score and Nutritional Parameters

Nutritional parameters	r value	p value
Serum albumin	-0.47	<0.001
nPCR	-0.32	<0.05
Subjective global assessment	-0.47	<0.01
Triceps skinfold thicknes	-0.40	<0.05
Midarm muscle circumference	-0.57	<0.01
Body mass index	-0.28	<0.05

2. Longitudinal study

Table 4 shows the baseline characteristic and the changes in the severity of depression, nutritional parameters, BIA and other clinical variables in the treatment and control groups. In the treatment group, mean age (52.5±11.2 versus 44.4±9.3, p<0.005) and proportion of diabetic patients (41.2% versus 14.3%, p<0.05) were higher than those of the control group. The baseline degrees of depression and malnutrition were higher in the treatment group compared to the control group. There was no difference in sex and duration of maintenance HD between two groups (data are

Table 4. Baseline Values and Changes in the Severity of Depression, Nutritional Status and Other Clinical Variables in the Treatment and Control Groups

	Treatment group (n=34)		Control group (n=28)	
	Baseline	8 weeks	Baseline	8 weeks
Severity of depression				
BDI	30.7±7.9*	not measured	13.0±6.4	not measured
HDRS	16.6±7.0	15.1±6.6†	not measured	not measured
SDS	59.2±10.9	56.0±12.6	not measured	not measured
Nutritional parameters				
Triceps skinfold thickness (mm)	8.2±2.8*	not measured	12.2±4.6	not measured
Midarm muscle circumference (cm)	20.7±2.1*	not measured	22.7±1.4	not measured
Body mass index (kg/m^2)	20.1±2.5	20.2±2.3	21.5±3.4	21.5±3.8
Subjective global assessment	4.03±1.24*	4.18±1.22	5.26±1.70	5.45±1.44
Serum albumin (g/dL)	3.73±0.20*	3.87±0.32†	4.15±0.41	4.16±0.43
BUN (mg/dL)	68.7±15.8	84.5±22.0†	75.4±16.0	79.7±18.5
nPCR (g/kg/day)	1.04±0.24*	1.17±0.29†	1.19±0.20	1.18±0.22
Bioimpedance analysis				
Intrcellular fluid volume (L)	19.7±3.6	20.1±3.6†	21.0±4.2	21.1±4.4
Extracellular fluid volume (L)	10.0±1.8*	9.6±1.6†	11.2±2.4	11.3±2.4
Lean body mass (kg)	42.9±7.5	42.9±7.3	46.4±8.8	46.3±9.2
Fat mass (kg)	8.9±4.2	9.1±4.1	9.6±3.9	9.6±4.0
Other clinical variables				
KT/Vurea	1.26±0.26	1.29±0.29	1.28±0.22	1.29±0.26
Bicarbonate (meq/L)	17.7±2.8	17.6±2.2	17.3±2.9	17.4±3.3
Hematocrit (%)	26.0±3.8	25.9±6.2	25.8±4.3	26.4±5.2
Post-hemodialysis weight (kg)	53.1±9.0	52.8±8.6	55.5±9.8	55.7±9.9
Inter-dialytic weight gain (kg)	2.25±0.97	2.29±1.97	2.22±1.01	2.37±1.62

Values are expressed as mean±SD unless otherwise note
**p<0.05 versus control group, †p<0.05 versus baseline values of treatment group*

not shown). Anti-depression treatment decreased HDRS score and increased nPCR, serum albumin and BUN concentration. Anti-depression treatment also induced slight but significant increase in intracellular fluid (ICF) volume and decrease in ECF volume measured by BIA. There was no significant change in KT/V_{urea}, plasma bicarbonate, hematocrit and interdialytic weight gain during anti-depression treatment. In the control group, no change was noted during the course of this study.

All patients successfully completed 8 weeks course of supportive psychotherapy and anti-depressant medication. Paroxetine was well tolerated by study patients and all patients successfully completed 8 weeks course of anti-depressant medication without evidence of major adverse events, even though 4 patients (8.3%) had mild central nervous symptoms (drowsiness, dizziness) during the study period.

Discussion

This study showed high incidence of depression and positive correlations between the severity of depressive symptoms and the degree of malnutrition in chronic HD patients. Anti-depression treatment reduced severity of depressive symptoms and increased nPCR, serum albumin and BUN concentration. It also significantly increased ICF volume measured by BIA. The hydration state of the ICF reflects water volume occupying the body cell mass, and the changes occur because of changes in the anabolic-catabolic state due to nutritional factors or illness[25]. Therefore the rise in ICF volume shown in this study could reflect increased anabolic state.

The positive correlation of depressive symptoms with the degree of malnutrition in ESRD patients might simply reflect a psychological response to a poorer overall medical condition.

However, there is some evidence that major depression is accompanied by activation of the inflammatory response system and that pro-inflammatory cytokines may play a role in the etiology of depression[26, 27]. The hyper-secretion of pro-inflammatory cytokines results in the malfunctioning of noradrenergic and serotonergic neurotransmission in the brain, changes which are reflected in the major symptoms of depression[11]. Pro-inflammatory cytokines which are commonly increased in ESRD patients are responsible for the increased protein catabolism, poor oral intake and malnutrition in maintenance HD patients[12]. Accordingly pro-inflammatory cytokines induced chronic inflammation could be a common cause of both depression and malnutrition in chronic HD patients.

It is also known that different classes of anti-depressants including selective serotonin-reuptake inhibitor reduce the release of pro-inflammatory cytokines from activated macrophages and increase the release of endogenous cytokine antagonists such as interleukin-1 receptor antagonist and interleukin-10[11, 28, 29]. Therefore, anti-depressants could reduce cytokine induced protein catabolism which will result in improvement of nutritional status in chronic HD patients. If anti-depressants reduce protein catabolism, increase in nPCR shown in this study means that anti-depression treatment significantly increased oral protein intake too. Accordingly both decreased protein catabolism and increased protein intake could be possible mechanisms of beneficial effect of anti-depression treatment shown in this study.

Paroxetine is a selective serotonin-reuptake inhibitor that was chosen because of its ease of administration (once-daily dosing), absence of active metabolites, and favorable side-effect profile, including lower levels of cardiotoxicity than those of tricyclic antidepressants[30]. However, initial dose of 10 mg was maintained without dose modification during the course of this study because of possible side effects and drug interac-

tions. This relatively small dose might be a cause of insignificant change in SDS score. And if longer duration and higher dose of paroxetine was used as needed, more significant changes in the severity of depression and nutritional parameters could be expected.

This study is limited by its small sample size and diagnostic dilemmas in patients with chronic HD which may be encountered because the somatic symptoms of uremia such as fatigue, anorexia, and sleep and bowel disorders are also important in establishing the diagnosis of depressive disorder.

We also excluded 14 patients who were uncooperative to our study or refused to answer our depression scale inventory. Because patients excluded from our study may have different clinical characteristics than enrolled patients, it is not clear whether our results can be generalized to excluded patients.

Our study population was recruited from the single outpatient HD unit in which all patients had intimate relationship with each other and most of patients who were diagnosed as depression wanted anti-depression treatment. Our anti-depression treatment included supportive psychotherapy in addition to anti-depressant medication. Therefore, we could not assign patients with depression to placebo treated control group.

In conclusion, our study suggests that in maintenance HD patients, depression is closely related with malnutrition and anti-depression treatment could improve nutritional status. Greater emphasis on the evaluation of and attempts to treat depression may be needed. Further confirmatory studies including measurement of cytokine levels are required to clarify the exact role of depression and its treatment with anti-depressant in the pathogenesis and management of malnutrition in chronic HD patients.

References

1) Kimmel PL, Weihs K, Peterson, RA : Survival in hemodialysis patients : the role of depression. *J Am Soc Nephrol* **4**:12-27, 1993
2) Finkelstein FO, Finkelstein SH : Depression in chronic dialysis patients : assessment and treatment. *Nephrol Dial Transplant* **15**:1911-1913, 2000
3) Kimmel PL : Psychosocial factors in adult end-stage renal disease patients treated with hemodialysis : correlates and outcomes. *Am J Kid Dis* **35**(suppl 1):132-140, 2000
4) Ruberman W, Weinblatt E, Goldberg JD, Chaudhary BS : Psychosocial influences on mortality after myocardial infarction. *N Engl J Med* **311**: 552-559, 1984
5) Covinsky KE, Kahana E, Chin MH, Palmer RM, Fortinsky RH, Landefield CS : Depressive symptoms and 3-year mortality in older hospitalized patients. *Ann Intern Med* **130**:563-569, 1999
6) Peterson RA, Kimmel PL, Sacks CR, Mesquita ML, Simmens SJ, Reiss D : Depression, perception of illness and mortality in patients with end-stage renal disease. *Int J Psychiatry Med* **21**:343-354, 1991
7) Kimmel PL, Peterson RA, Weihs KL, et al. : Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis patients. *Kidney Int* **57**:2093-2098, 2000
8) Lopes AA, Bragg J, Young E, et al. : Dialysis Outcomes and Practice Patterns Study (DOPPS). Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe. *Kidney Int* **62**:199-207, 2002
9) Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM : The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* **329**:1001-1006, 1993
10) Dantzer R : Cytokine-induced sickness behavior : Where do we stand? *Brain Behav Immun* **15**:7-24, 2001
11) Leonard BE : The immune system, depression and the action of antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry* **25**:767-780, 2001
12) Stenvinkel P, Barany P, Heimburger O, Pecoits-Filho R, Lindholm B : Mortality, malnutrition, and atherosclerosis in ESRD : What is the role of

interleukin-6? *Kidney Int* **61**(suppl 80):103-108, 2002

13) Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J : An inventory for measuring depression. *Arch Gen Psychiatry* **4**:561-571, 1961

14) Beck AT, Steer RA, Garbin MG : Psychometric properties of the beck depression inventory : twenty-five years of evaluation. *Clin Psychol Rev* **8**:77-100, 1988

15) Kimmel PL, Peterson RA, Weihs KL, et al. : Psychosocial factors, behavioral compliance and survival in urban hemodialysis patients. *Kidney Int* **54**:245-254, 1998

16) Hahn HM, Yun TH, Shin YW, Kim KH, Yoon DJ, Chung KJ : A standardization study of Beck Depression Inventory in Korea. *J Korean Neuropsychiatr Assoc* **25**:487-502, 1986

17) CANADA-USA (CANUSA) Peritoneal Dialysis Study Group : Adequacy of dialysis and nutrition in continuous peritoneal dialysis : Association with clinical outcomes. *J Am Soc Nephrol* **7**:198-207, 1996

18) Chumlea WC, Guo SS, Vellas B : Assessment of protein-calorie nutrition, in Kopple JD, Massry SG (eds.) : Nutritional management of renal disease, chap 7. Baltimore, MD, Wiliams & Wilkins, 1997, p203-228

19) Zoccali C, Postorino M : Electronic publishing : now and tomorrow. *Nephrol Dial Transplant* **13**(suppl 1):25-29, 1998

20) Hamilton M : A rating scale for depression. *J Neurol Neurosurg Psychiatry* **23**:56-62, 1961

21) Zung W : A self-rated depression scale. *Arch Gen Psychiatry* **12**:63-70, 1965

22) Cha K, Chertow GM, Gonzalez J, Lazarus JM, Wilmore DW : Multifrequency bioelectrical impedance estimates the distribution of body water. *J Appl Physiol* **79**:1316-1319, 1995

23) Zhu F, Schneditz D, Wang E, Martin K, Morris AT, Levin NW : Validation of changes in extracellular volume measured during hemodialysis using a segmental bioimpedance technique. *ASAIO J* **44**:M541-545, 1998

24) Song JH, Lee SW, Kim GA, Kim MJ : Measurement of fluid shift in CAPD patients using segmental bioelectrical impedance analysis. *Perit Dial Int* **19**:386-390, 1999

25) Mehta RL, Jaeger JQ : Dry weight and body composition in hemodialysis : a proposal for an index of fluid removal. *Semin Dial* **12**:164-174, 1999

26) Maes M : Major depression and activation of the inflammatory response system. *Adv Exp Med Biol* **461**:25-46, 1999

27) Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H : Cytokine production and serum proteins in depression. *Scand J Immunol* **41**:534-538, 1995

28) Xia Z, De Poere JW, Nassberger L : TCA's inhibit IL-1, IL-6 and TNF release in human blood monocytes and IL-2 and interferon in T-cells. *Immunopharmacol* **34**:27-37, 1996

29) Suzuko E, Shintani F, Kamba S, Asai M, Nakaki T : Induction of interleukin-1 beta and intedeukin-1 receptor antagonist mRNA by chronic treatment with various psychotropics is widespread areas of rat brain. *Neurosci Let* **215**:201-204, 1996

30) Leonard BE : Pharmacological differences of serotonin reuptake inhibitors and possible clinical relevance. *Drugs* **43**(suppl 2):3-9, 1992