# Interleukin-2 Receptors In Childhood Depression

*Thesis*

*Submitted for the Fulfillment*
*Of the Degree of Doctor*
*Of philosophy in Childhood studies*

**Wafaa Mostafa El-Genaidy**

*(M.B., B. Ch., M. Sc. In Childhood Studies, M.Sc. in Pediatrics, Ain Shams University*

***Under Supervision of***

**Prof. Dr. Adel El-Messiry**
*Professor and Head of Medical Research Centre*
*Ain Shams University*

**Prof. Dr.Naglaa El-Mahalawy**
*Professor of Psychiatry*
*Ain Shams University*

**Prof. Dr. Olweya M.Abd El-Baky**
*Professor in Pediatric Psychiatry*
*Childhood Studies*
*Ain Shams University*

**Assis. Prof. Dr. Randa Abdel Wahab Reda Mabrouk**
*Assistant Professor in Clinical Pathology*
*Ain Shams University*

***Ain Shams University***
***Institute Of Post Graduate Childhood Studies***
***2001***


بسم الله الرحمن الرحيم

# Acknowledgement

First, thanks God for helping me to finish this study. Then I would like to express my deep gratitude to **Prof. Adel El-Messiry**, Professor and head of Medical Research Center, Ain Shams University, not only for his care, but also for the valuable advice, encouragement and the help he gave me.

I am also very grateful to **Prof. Naglaa El-Mahalawy**, ***Professor of Psychiatry, Ain Shams University*** for her guidance, corrections, explanations and provision of support.

Special thanks go to **Dr. Olweya M. Abd El-Baky**, ***Professor in Pediatric Psychiatry medical department of Postgraduate Institute of Childhood Studies, Ain Shams University***, for her understanding, careful and continuous guidance and meticulous revision and correction. To thank her, would fall short of how I feel for her.

I am also very thankful to **Dr. Randa Abd-El-Wahab Reda Mabrouk**, ***Assistant Professor in Clinical Pathology, Ain Shams University*** for her great help and support from the beginning to the end of this thesis.

I would like also to express my gratitude to **Prof. Afaf Hamed Khalil**, ***Professor of Psychiatry, Ain Shams University***, who helped me a lot in writing the protocol of this thesis.

I am very very thankful to **Dr. Nahla El-Said Nagy**, ***Lecturer of Psychiatry, Ain Shams University,*** who helped a lot and encouraged me a lot. Without her help I would not have finished this thesis at all.

I am also thankful to **Dr. Madiha Ahmed Omar**, *Fellow of Clinical Pathology, Medical-Research Center, Ain Shams University*, for helping me in doing the practical work of this thesis.

For my mother and father, I will always be indebted.

Finally, my thanks extend to patients of the department of psychiatry, Ain Shams University.

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# List of Abbreviations

| | |
|---|---|
| ACTH | Adrenocoticotrophic hormone. |
| ADHD | Attention deficit hyperactivity disorder. |
| AIDS | Acquired immune deficiency syndrome. |
| ANOVA | Analysis of variance. |
| APP | Acute phase protein |
| BUP | Bupropion |
| CBT | Cognitive behavioral therapy |
| CD | Cluster of differentiation antigen |
| CDI | Children depression inventory |
| CMI | Clomipramine |
| CMI | Cell mediated immunity |
| CNS | Central nervous system |
| CRH | Corticotropin-releasing hormone |
| DHEA | Dehydro-epiandrosterone |
| DMI | Desipramine |
| DMP-1 | Diagnostic manual of psychiatric disorders no.1 |
| DPP IV | Dipeptidyl peptidase IV |
| DSM III | Diagnostic and statistical manual of mental disorders, third edition. |
| DSM IV | Diagnostic and statistical manual of mental disorders, fourth edition. |
| DSM III R | Diagnostic and statistical manual of mental disorders third edition, revised. |
| DST | Dexamethasone suppression test. |
| ECS | Electroconvulsive shock |
| ECT | Electroconvulsive therapy |
| ELISA | Enzyme linked immunosorbent assay. |
| GABA | Gamma aminobuteric acid. |

| | |
|---|---|
| G-CSF | Granulocyte-colony stimulating factor |
| GH | Growth hormone |
| GM-CSF | Granulocyte, monocyte-colony stimulating factor. |
| HAD | Hospital anxiety and depression. |
| HDL | High density lipoprotein |
| HLA | Human leukocyte antigen |
| HPA | Hypo-thalamic-pituitary-adrenal axis. |
| ICD-9 | International classification of mental and behavioural disorders number 9. |
| ICD-10 | International classification of mental and behavioural disorders number 10. |
| IFN | Interferon |
| IL | Interleukin |
| IL-2R | Interleukin-2 receptor |
| IL-2R $\alpha$ | Interleukin-2 receptor alpha |
| IL-2R $\beta$ | Interleukin-2 receptor beta |
| IL-2R $\gamma$ | Interleukin-2 receptor gamma |
| IL-2R $\gamma_c$ | Interleukin-2 receptor gamma common chain |
| IP-10 | Inhibitor protein number 10 |
| JAK | Janus protein tyrosine kinase |
| Kd | Kilodalton |
| LAK | Lymphokine activated killer activity. |
| LTT | Lymphocyte transformation test |
| MAOIs | Mono amine oxidase inhibitors |
| MAP | Mitogen-activated protein kinase. |
| M-CSF | Monocyte-colony stimulating factor. |
| MCP-1 | Monocyte chemotactic peptide 1 |
| MDD | Major depressive disorder |
| MHC | Major histocompatability. |

| | |
|---|---|
| **MIF** | Migration inhibition factor |
| **MIP1α** | Macrophage inflammatory protein-1α |
| **MIRT** | Mirtazapine |
| **NE** | Norepinephrine |
| **NEF** | Nefazodone |
| **NKC** | Natural killer cell |
| **NST** | Nondirective supportive therapy |
| **OCD** | Obsessive compulsive disorder |
| **PBMC** | Peripheral blood mononuclear cells. |
| **Pg** | Picrogram |
| **RANTES** | Regulated upon activation normally T cell expressed and secreted. |
| **R-MAOIS-A** | Reversible monoamine oxidase inhibitors selective for monoamine oxidase A. |
| **SBFT** | Systemic behavioral family therapy |
| **SNS** | Sympathetic nervous system. |
| **SOCS** | Suppressor of cytokine signaling |
| **SSI** | Signal transducer and activator of transcription (STAT) induced STAT inhibitor. |
| **SSRI** | Selective sertotonin reuptake inhibitor |
| **STAT** | Signal transducer and activator of transcription |
| **TAC** | T cell activator |
| **TCA** | Tricyclic antidepressant |
| **TGF** | Tumour growth factor |
| **TNF** | Tumour necrosis factor |
| **VLF** | Venlafaxine |

# *Abstract*

***Researcher's Name:*** **Wafaa Mostafa Mohamed El-Genaidy.**

***Title:*** **Interleukin-2 Receptors in Childhood Depression.**

***Place of study:*** **Institute of post graduate childhood studies-Ain Shams University.**

***Abstract:*** A sample of 60 Egyptian depressed patients, 7-18 years old, were selected from the Institute of Psychiatry, Faculty of medicine, Ain Shams University by ***ICD-10 (1992)***. They were subclassified into three groups (20 each) according to the severity of depression.

Cases (no=60) and controls (no=20) were subjected to: psychiatric interview, complete physical examination, children depression inventory (CDI), and a questionnaire for socioeconomic level (EL-Shakhs, 1995), and finally serum was used for detection of soluble interleukin-2 receptor (sIL-2R) using enzyme linked immunosorbent assay (ELISA).

The results of this study showed that females were significantly more than males.

There was a high significant difference between cases and controls as regard loss of one or two parents, also as regard maternal psychopathology.

Soluble IL-2R levels in serum were significantly increased in depressed patients and was positively related to the severity of depression.

Soluble IL-2R was significantly positively related to male sex, and was significantly related to maternal psychopathology only in severe group of depression.

Severe sleep disturbance significantly affects the level of sIL-2R.

Further studies are needed to set reference values for sIL-2R and to know why sIL-2R is more in males with severe depression than females.

***Key words:***

Depression/Childhood depression / IL-2 / IL-2R / sIL-2R Immunology of depression.

# *Introduction and aim of the study*

# INTRODUCTION

Depression may be comorbid, disabling syndrome that affects approximately 2-7% of children, 3-10% of adolescents *(Eid, 1998)*, and approximately 15-25% of cancer patients *(Henriksson, et al., 1995)*.

Some people may develop depression while sick with chronic illness and immune related disorders such as acquired immune deficiency syndrome (AIDS) and certain cancers *(Johnson et al, 1999)*.

However, recent developments in psychoneuro-immunology suggest that major depression and stressful life events may increase the susceptibility to diseases or prolong existing medical problems by means of aberration occurring within the immune system *(Mendlovic et al, 1997)*.

Some researchers reported that depression is accompanied by in vitro immune-suppression as indicated by lymphocyte transformation tests, lower number of T and B cells and diminished natural killer cell activity *(Hickie et al, 1993 and Schleifer et al, 1996)*.

Results of flow cytometric analysis have shown that depression is characterized by increased cluster of differentiation (CD) antigen and increased $CD4^+$/ $CD8^+$ cell ratio *(Maes et al, 1992)*.

It has been reported that depression is characterized by T-cell activation which is manifested by significantly increased number and percentage of activated T- lymphocytes, interleukin-2 receptors bearing cells and human leukocyte antigen (HLA) DR+Tcells and increased level of soluble interleukin-2 receptor which is another marker of T cell activation *(Maes et al., 1995a)*.

# Aim of the study

This study attempts to investigate the most common symptomatology in different categories of depression (mild, moderate, and severe). It also aimed to study interleukin-2 receptors. in depressed children according to the various degrees of severity of the disorder.

# *Review of Literature*

***Chapter One:***

# *Childhood Depression*

# REVIEW OF LITERATURE
# CHILDHOOD DEPRESSION

## Definition of Depression:

Depressed mood or affect refers to a state of dysphoria that occurs frequently in the course of normal development. It is part of negative feelings, but lack of positive affect and a loss of emotional involvement with other people, objects or activities constitute specific features that distinguish depressed mood from normal feelings of sadness or demoralization and from other negative affects such as anxiety. Youths with depression often have significant interpersonal, intrafamilial and academic difficulties *(Findling et al., 2000; Fombonne, 1994)*.

Depressive syndrome refers to a constellation of observable symptoms (of which depressed mood is only one component) such as tearfulness, irritability, death thoughts, loss of appetite, disturbance of sleep, lack of energy, ..... etc. that tend to cluster together. At the individual level, a depressive syndrome is recognized when the behavioral characteristics reach a given threshold that signals a significant deviation from the norm *(Fombonne, 1994)*.

## Epidemiology of depression:

It was once thought that children could not become depressed due to immaturity of their psyche. Recent studies, however show that 7 to 14 percent of children will have a major depressive episode before age fifteen *(Quinn, 1997)*.

In Arabic countries, Egypt, ***Abdel Baki et al., (1992)*** found 2 female cases out of 30 (15from each sex) have major depression following DSM III R criteria.

In western countries, according to ***Trangkasombat and Likanapichikul, (1997)*** who examined 81 children who came to

the out- patient pediatric clinic, there were 39 boys and 42 girls with a mean age 10years. The results of the study were as follows : The prevalence of depression was 34.6%. **Types of depression were:** 7.4% depression symptoms only, 17.3% adjustment disorder with depressed mood, 6.2% dysthymia, 3.7% major depression. Females had more severe symptoms than males. However ***Bebbington et al., (1998)*** deduced that the sex difference in depressive disorders is absent in children. Of the depressed group 60.7% had previous suicidal behavior compared with 20.6% in the non depressed group. The rates of all psychosocial stressors were higher in the depressed group. Those of statistical significance were:

* Parental psychiatric illness.

* Unstable living condition.

* History of abuse.

The same study also shows that depression is prevalent in children with physical illness ***(Trangkasombat and Likanapichitkul, 1997)***. ***Henriksson et al., (1995)*** stated that depression affects approximately 15% to 25% of cancer patients.

***Wilson et at. (1995)*** found that 5% of children have depression.

***Birmaher et al., (1996)*** studies also show that persons born in the latter part of the 20$^{th}$ century are at greater risk for developing mood disorders, and at a younger age.

Lower social class is associated with a greater number of provoking agents and it is thought that this allows vulnerability factors to act more powerfully than in a middle class population ***(Berney et al., 1991)***. The level of parental education for the depressed children is unusually high. Depression may be more common in rural areas than in urban areas ***(Kaplan and Sadock, 1991)***.

## Classification of Depression:

It is 25 year since ***Kednell, (1976)*** reviewed the temporary confusion surrounding the classification of depression. reconsideration of this issue is now essential especially in light of the development of the other classifications of depressive disorder included in ***DSM-III (1980***, the revised version, ***DSM-III-R (1987), ICD-9 (1978), DMP-1 (1979), DSM-IV (1994), and ICD-10 (1992)***, which are shown in table (1),(2) and (3).

**Table (1): Classifications of mood (affective) disorders:**

| DSM III (1980) | DSM III-R (1987) | ICD-9 (1978) | DMP-1 (1979) |
|---|---|---|---|
| * Major affective disorder:<br>- Manic episode<br>- Depressed episode<br>- Mixed | * Bipolar disorders:<br>- Manic episode or hypomanic<br>- Depressed<br>- Mixed | *Affective Psychosis<br>- Manic type<br>- Depressed type<br>- Circular type | Manic and depressive illness:<br>1. Manic type<br>2. **Depressive type**<br>3. Circular type<br>4. Mixed type<br>5. Involutional<br>6. Depressive illness not elsewhere classified<br>7. Manic illness not elsewhere specified<br>8. Others. |
| ***Major depression:**<br>- **Single episode.**<br>- **Recurrent** | ***Major depression:**<br>- **Single.**<br>- **Recurrent.** | | |
| * Other specific affective disorder<br>- Cyclothymia.<br>- Dysthymia | - Cyclothymia.<br>- Dysthymia (depressive neurosis | * Other non-organic psychosis of depressive type:<br>- Neurotic depression<br>- Depressive disorder not elsewhere classified. | |
| * Atypical affective disorder | *Adjustment disorder with depressed mood. | | |

**Table (2): DSM-IV Classification of mood (affective) disorder**

| DSM-IV (1994) |
|---|
| **A- Depressive disorder:** |
| 1- **Major depressive disorder, single episode, recurrent** |
| 2- Dysthymic disorder |
| 3- Not other specified. |
| **B- Bipolar disorder:** |
| **I- Bipolar I:** |
| 1- Single manic episode |
| 2- Most recent episode (hypomanic, manic, mixed, depressed, unspecified |
| **II- Bipolar II:** |
| Specify (current or most recent episode ) as hypomanic, depressed |
| **III- Cytothymic disorder.** |
| **IV- Bipolar disorder (Not other specified)** |
| **V. Mood disorder due to general medical condition:** |
| 1- Specify type with depressive-like episode with manic features, with mixed features. |
| 2- Substance induced mood disorder. |
| 3- Mood disorder (non-specified). |

## Table (3): ICD-10 classification of mood (affective) disorders

**F30 Manic episode**

F30.0 Hypomania

F30.1 Mania without psychotic symptoms

F30.2 Mania with psychotic symptoms

F30.8 Other manic episodes.

F30.9 Manic episode, unspecified.

**F31 Bipolar affective disorder**

F31.0 Bipolar affective disorder, current episode hypomanic

F31.1 Bipolar affective disorder, current episode manic without psychotic symptoms

F31.2 Bipolar affective disorder, current episode manic with psychotic symptoms

F31.3 Bipolar affective disorder, current episode mild on moderate depression

.30 Without somatic symptoms

.31 With somatic symptoms

F31.4 Bipolar affective disorder, current episode severe depression without psychotic symptoms.

F31.5 Bipolar affective disorder, current episode severe depression with psychotic symptoms.

F31.6 Bipolar affective disorder, current episode mixed.

F31.7 Bipolar affective disorder, currently in remission.

F31.8 Other bipolar affective disorders.

F31.9 Bipolar affective disorder, unspecified.

**F32 Depressive episode**

**F32.0 Mild depressive episode**

**.00 Without somatic symptoms**

**.01 With somatic symptoms**

**F32.1 Moderate depressive episode**

**.10 Without somatic symptoms**

**.11 With somatic symptoms**

**F32.2 Severe depressive episode without psychotic symptoms**

**F32.3 Severe depressive episode with psychotic symptoms**

**F32.8 Other depressive episodes**

**F32.9 Depressive episode, unspecified.**

## Table (3) (cont.): ICD-10 classification of mood disorders

**F33 Recurrent depressive disorder**

F33.0 Recurrent depressive disorder, current episode mild

.00 Without somatic symptoms

.01 With somatic symptoms

F33.1 Recurrent depressive disorder, current episode moderate

.10 Without somatic symptoms

.11 With somatic symptoms

F33.2 Recurrent depressive disorder, current episode severe without psychotic symptoms

F33.3 Recurrent depressive disorder, current episode severe with psychotic symptoms.

F33.4 Recurrent depressive disorder, currently in remission.

F33.8 Other recurrent depressive disorders.

F33.9 Recurrent depressive disorder, unspecified.

**F34 Persistent mood [affective] disorders**

F34.0 Cyclothymia

F34.1 Dysthymia

F34.8 Other persistent mood [affective] disorders

F34.9 Persistent mood (affective] disorder, unspecified.

**F38 Other mood [affective] disorders**

F38.0 Other single mood [affective] disorders

.00 Mixed affective episode

F38.1 Other recurrent mood [affective] disorders

.10 Recurrent brief depressive disorder

F38.8 Other specified mood [affective] disorders

**F39 Unspecified mood [affective] disorder**

*(ICD10,1992).*

## Depressive episode

The sample of this study was diagnosed by *ICD-10 (1992)* (Table 3) that is why it will be described here in details.

In *ICD-10 (1992)* typical depressive episodes of all three varieties (mild, moderate, and severe), the individual usually suffers from:

- Depressed mood.
- Loss of interest and enjoyment.
- Reduced energy leading to increased fatigability and diminished activity (marked tiredness after only slight effort is common).

Other common symptoms are:

a) Reduced concentration and attention.

b) Reduced self-esteem and self-confidence

c) Ideas of guilt and unworthiness (even in a mild type of episode).

d) Bleak and pessimistic views of the future.

e) Ideas or acts of self-harm or suicide

f) Disturbed sleep.

g) Diminished appetite.

A duration of at least 2weeks is usually required for diagnosis, but shorter periods may be reasonable if symptoms are unusually severe and of rapid onset.

Somatic symptoms such as:

- Loss of interest or pleasure in activities that are normally enjoyable.
- Lack of emotional reactivity to normally enjoyable surroundings and events.

- Waking in the morning 2hours or more before the usual time,
- Depression worse in the morning.
- Objective evidence of definite psychomotor retardation or agitation.
- Marked loss of appetite.
- Weight loss (5% or more of body weight in the past month).
- Marked loss of libido.

Usually, this somatic syndrome is not regarded as present unless about four of these symptoms are definitely present.

**Mild depressive episode:**

In order to diagnose mild depressive episode two of the following symptoms must be present: Depressed mood, loss of interest and enjoyment, and increased fatigability. Plus at least two of the other common symptoms of depression described before.

None of the symptoms should be present to an intense degree. An individual with a mild depressive episode is usually distressed by the symptoms and has some difficulty in continuing with ordinary work and social activities, but will probably not cease to function completely. A fifth character may be used to specify the presence of a somatic syndrome either with or without somatic syndrome.

**Moderate depressive episode:**

At least two of the three most typical symptoms noted for mild depressive episode should be present, plus at least three of the other symptoms. Several symptoms are likely to be present to a marked degree, but this is not essential if a particularly wide variety of symptoms is present overall. There is considerable difficulty in continuing with social work or domestic activities. A fifth character may be used to specify the occurrence of a somatic syndrome: i.e. with or without somatic syndrome.

**Severe depressive episode without psychotic symptoms:**

There is considerable distress or agitation, unless retardation is a marked feature. Loss of self-esteem or feelings of uselessness or guilt are likely to be prominent, and suicide is a distinct danger in particularly severe cases. It is presumed here that the somatic syndrome will almost always be present in a severe depressive episode.

All three of the typical symptoms noted for mild and moderate depressive episodes should be present, plus at least four other symptoms some of which should be of severe intensity. However, if important symptoms such as agitation or retardation are marked, the patient may be unwilling or unable to describe many symptoms in details. An overall grading of severe episode may still be justified in such instances.

It is very unlikely that a patient with severe depressive episode will be able to continue with social, work, or domestic activities, except to a very limited extent.

**Severe depressive episode with psychotic symptoms:**

A severe depressive episode which meets the criteria given above and in which delusions, hallucinations or depressive stupor are present. The delusions usually involve ideas of sin, poverty or imminent disasters, responsibility for which may be assumed by the patient. Auditory or olfactory hallucinations are usually of defamatory or accusatory voices or of rotting filth or decomposing flesh. Severe psychomotor retardation may progress to stupor.

**Other depressive episodes:**

Includes fluctuating mixtures of depressive symptoms (particularly the somatic variety) with non diagnostic symptoms such as tension worry, and distress, and mixtures of somatic depressive symptoms with persistent pain or fatigue not due to organic causes (as sometimes seen in general hospital services).

## Etiology of depression

**1. Genetic Factors**

**2. Biological Factors:**

**A. Biogenic amines.**

- Serotonin
- Noradrenaline

**B. Neuroendocrine Regulation:**

- Hypothalamic-Pituitary –Adrenal (HPA) Axis.
- Cortisol, prolactin and Growth Hormone.

**C. Cytokines**

**D. Other biological data : Cholosterol**

**3. Psychological Factors**

## 1. Genetic Factors:

***Demerdash et al., (1995)*** studied 20 cases of mood disorders with positive family history, all cases were subjected to clinical assessment and diagnosis according to DSM-III-R, psychological investigation and genetic assessment with pedigree construction. Statistical analysis for recurrence risk in relatives was calculated. This study confirms the genetic basis of mood disorder and gives an Egyptian emperic recurrence risk for the relatives ranging from 9.1 up to 25%, this was correlated with the severity of illness in respect to the number of hospitalization and age of onset. The mode of inheritance was confirmed by statistical analysis to be polygenic or multifactorial mode of inheritance.

***Weller et al., (1994)*** stated that the presence of MDD and any type of mood disorder was significantly greater in families of children with MDD than psychiatric control group. ***Cantwell***

*(1996)* found that mothers of the depressed children were much more likely to be clinically depressed than fathers.

***Warner et al (1995$_b$)*** suggested that recurrent parental major depressive disorder increases the risk of both offspring major depressive disorder and anxiety disorder. Also ***Warner et al, (1995$_a$)*** results are compatible with the genetic model in which depression in parents is caused by a factor which can be expressed as depression or anxiety in offspring.

***Todd et al., (1996)*** found that the risk for developing major depressive disorder or mania if you have an affected parent is greater than if you have healthy parents but an affected second degree relative is much greater than if you have healthy first and second degree relatives but an affected third degree relative is much greater than if you have healthy first, second, and third degree relative.

***Cadoret et al., (1996)*** results suggest that depression spectrum disease has as one of its principal etiologic factors a gene-environment interaction and that relatives of patients with early-onset depression were more likely to be depressed if they were female and more likely to be alcoholic or antisocial if they were male.

***Warner et al., (1992)*** found that the offspring exposed to two or more episodes of parental depression had onset of MDD before the age of 14 years.

## 2. Biological Factors:

### A. Biogenic Amines:

- **Serotonin:**

***Ryan et. al., (1992)*** discussed their results as consistent with a dysregulation of central nervous system serotonin functioning in depressed children. Also ***Kutcher and Matron (1994)*** suggest that child and adolescent onset of major depression may be primarily a result of serotonergic dysregulation.

- **Noradrenaline:**

In adult urine studies of noradrenaline metabolite (3-methoxy-
4-hydroxy phenylethylene glycole) indicated that depressed patients had low level of this metabolite when compared to normal *(Rothschild, 1988)*. However, no significant differences were found between groups of MDD and normal controls suggesting relatively intact noradrenergic system in children *(Kutcher and Marton, 1994)*.

**B. Neuroendocrine regulation:**

- **Hypothalamic- pituitary- adrenal (HPA) axis:**

Comprehensive evolutions of the hypo-thalamic- pituitary-adrenal (HPA) axis in depressed adolescents have not replicated the findings of HPA dysregulation commonly found in studies of adult depressives i.e. the basal HPA activity is not dysregulated in children and adolescents *(Kutcher and Marton, 1994)*.

- **Cortisol, prolactin and growth hormone:**

*Ryan et al. (1992)* found the depressed children showed significantly less secretion of cortisol and significantly more prolactin secretion than controls. Growth hormone (GH) secretion did not differentiate the groups.

However *(Goodyer et al., 2000)* deduced that depression in adolescents is associated with high evening cortisol and low morning dehydroepiandrosterone (DHEA) concentration in about 40% of adolescent group, and that variations in adrenal steroid function are not simply a consequence of MDD but indicate a potential contribution of the steroid milieu to the onset of first episode disorder in adolescents.

**C. Cytokines:**

(It will be discussed later in details in another chapter).

Several lines of evidence indicate that brain cytokines, principally interleukin 1 beta (IL-1beta) and IL-1 receptor

antagonist may have a role in the biology of major depression, and that they might additionally be involved in the pathophysiology and somatic consequences of depression as well as in the effects of antidepressant treatment (Licinio, and Wong, 1999).

Administration of proinflammatory cytokines including tumor necrosis factor (TNF) alpha, IL-1 and IL-6 have been shown in humans and laboratory animal to lead to a syndrome of sickness behavior which shares many features in common with major depression e.g. anhedonia, fatigue, anorexia poor concentration, social isolation, altered sleep pattern (Miller, 2000).

Proinflammatory cytokines have been shown to have potent stimulatory effects on the hypothalamic-pituitary-adrenal (HPA) axis with the resultant release of glucocorticoids. The effects of these cytokines on the HPA axis are mediated in large part by the induction of corticotropin-releasing hormone (CRH), CRH increases secretion of glucocorticoids.

***Miller et al. (1999)*** also suggest that cytokines have the capacity to contribute to glucocorticoid resistance and thus the pathophysiology of depression.

Resistance to HPA axis suppression by dexamethasone as manifested by an abnormal dexamethasone suppression test (DST) is another prominent feature of the neuroendocrine alterations in depression. Evidence indicates that proinflammatory cytokines are also capable of disrupting the function of glucocorticoid receptors that in turn are responsible for dexamethasone-mediated feedback inhibition. For example treatment of cells in vitro with IL-1 alpha has been found to block translocation of the glucocorticoid receptor from cytoplasm to nucleus and decrease dexamethasone induction of glucocorticoid-receptor-mediated gene transcription. In addition, treatment of rats with bacterial endotoxin, a potent inducer of pro-inflammatory cytokines cause both sickness behavior and dexamethasone nonsuppression ***(Miller, 2000)***.

Over the years a body of evidence has been accumulated suggesting that major depression is associated with dysfunction of inflammatory mediators. Major depression commonly co-occurs with ischemic heart disease and decreased bone mineral density. Depressive symptoms are known to have a negative impact on cardiovascular prognosis increasing the mortality rate of coronary artery disease ***(Licinio and Wong, 1999)***.

Depression has been hypothesized to be related to the reduced biosynthesis of neurotransmitters such as serotonin, noradrenaline and dopamine. Administration of cytokines and cytokine inducers have been found to lead to changes in the turnover of relevant monoamines including serotonin, norepinephrine and dopamine in key brain regions such as the hypothalamus and hippocampus ***(Miller, 2000)***. Van-Amsterdam and Opperhuizen, (1999) review the evidence linking tetrahydrobiopterin, a cofactor in the biosynthesis of neurotransmitters, and nitric oxide, an apparent neuroendocrine modulator of the hypothalamic-pituitary-adrenal (HPA), axis, to the immune system and to neuronal control with affective disorder and stress.

**D. Other biological data:**

- **Cholesterol:**

A low content of cholesterol within cell membranes has been shown experimentally to decrease the number of serotonin receptors; and it has been hypothesised that lowered levels of serum total cholesterol may lead to a decrease in brain serotonin and as a consequence, to poor control of aggressive impulses. The low serum total cholesterol predicts the occurrence of more severe conditions indicative of poor outcome, such as hospitalisations due to major depressive disorder and death from suicide ***(Partonen et al., 1999)***.

## 3. Psychological factors:

***Williamson et al., (1998)*** reported that depressed adolescents were significantly more likely to have had two or

more refined severe stressful events prior to becoming depressed (50versus 0%) compared with normal controls. Therefore, clinical efforts focused on providing clinical intervention soon after occurrence of the first severe event might help to prevent the onset of depression in adolescents.

The severe events in this sample of adolescents included the following :

Close friend moving away, first sexual intercourse, becoming pregnant , having an abortion, friend being raped, sister returning home to live, being sexually annoyed by a stranger, argument and breakdown in relationship with mother, and a fight at school, mother having surgery for breast cancer, father being involved in a car accident and taken by ambulance to the hospital, death of an uncle, exboyfriend shooting another person, and classmate being killed in an automobile accident ***(Williamson et al., 1998)***.

Also ***Hammen et al., (1999)*** argued that depression commonly occurs in a highly problematic interpersonal and environmental context that typically is not adequately addressed by existing treatments. The data demonstrated that **the children's families were characterized by high rates of psychopathology in both parents** as well as maternal intergenerational patterns of diagnosis, assortive mating, and marital dysfunction, plus high rates of exposure to stressful life events. In addition, the children typically displayed comorbid diagnoses. Substantial proportions functioned poorly both socially and academically, reflecting not only impairment but also significant sources of stress that the children are typically ill-equipped to handle.

While maternal depression among samples of depressed youth is well documented, less attention has been granted to the need to treat such women owing to their critical and unresponsive interactions with children that might contribute to the youngsters own depression ***(Kaslow et al., 1994)***. Also, depressed mothers, especially those whose own parents may have been psychiatrically impaired, may model dysfunctional problem-

solving skills and may be unavailable to help children buffer the ill effects of stress *(Hammen et al., 1991)*.

Moreover the finding that the siblings and the fathers of depressed youngsters also had significant psychiatric problems further challenges current treatments. Certainly one implication of assortive mating is marital distress, which was observed in abundance in the current sample. Marital discord has been shown to be a significant contributor to children's maladjustment generally and is hypothesized to be a mechanism of transmission of negative outcomes in children of depressed parents *(Downey and Coyne, 1990)*.

A final implication of ***Hammen, et al, (1999)*** is that depressed children are also exposed to considerable stress. Their mothers show elevated stress levels, and the youngsters themselves have relatively high rates of both chronic and episodic stress. These stresses, children's social isolation or conflict, and academic failure or inability to handle typical school environments would challenge the skills of healthy children, much less those with deficient coping capabilities and resources. Moreover, children with clinically significant depression might be at risk for actually contributing to stress occurrence, likely through maladaptive academic and social skills and conflict-laden family and personal relationships *(Adrian and Hammen, 1993)*.

**Comparison between pathogenesis of adult and childhood Depression:**

There are more similarities than dissimilarities in carefully diagnosed children and adolescents with persistent major depression compared with adults. Patients with onset of depression at a younger age have more similarities than dissimilarities to depressed adults. The same criteria (i.e. DSM-IV) are generally used to diagnose depression in children, adolescents and adults, although the process of eliciting symptoms is different. Developmental differences and brain maturation probably affect the expression of these underlying mechanisms. For example dexamethasone non suppression has

been extensively reported in depressed children and adolescents, but 24-hour or nocturnal hypercortisolemia is not found consistently. Rapid eye movement sleep abnormalities similar to those in adults have been found in some samples of depressed children and adolescents, though they are less robust than in adults. Differences in the results of growth hormone challenge tests in children are similar to those in adults. However the response of depressed children and adolescents to tricyclic antidepressants (TCA) has been different ***(Emslie, et al., 1999)***.

## Clinical Picture of depression

The clinical picture of depression in children some what parallels that of adults, except that children are more likely to present with separation anxiety, phobias, somatic complains, and behavioral problems ***(Dalton and Forman, 2000)***.

## Symptoms of Depression in Children:

1. They act badly or are irritable for no apparent reason. They have little frustration tolerance. They are demanding and difficult to please, and they complain about everything. Nothing makes them happy.
2. They frequently look sad, tired or ill. They may by tearful. They do not seem to have the usual amount of childhood energy and curiosity, or they lack the sense of humor and fun that most children have.
3. They say they do not feel good, or they complain of stomachaches, headaches or other physical illnesses.
4. They are easily stressed out and over- whelmed and tend to worry a lot or have exaggerated fears.
5. They get upset when separated from their parents. They become increasingly clingy and dependent. They may start acting babyish again, sucking their thumb or wetting their pants.
6. They are losing interest in activities they used to enjoy, such as club attendance or sports.
7. They are very shy or have difficulty making friends. They are nervous about interacting with or performing in front of others.
8. Their grades are declining.
9. They talk about death and dying.
10. Their appetite changes.
11. Not sleeping or sleeping too much.

12. Feelings of worthlessness.
13. Self-criticism.
14. Inappropriate guilt.
15. Inability to think or concentrate well.
16. Depression should be considered whenever any behavior problem persists *(Quinn, 1997; PDQ, 2000)*.

## Symptoms of Depression in Adolescents:

1. They are ill-tempered "touchy" or overactive and difficult to get along with.
2. They are aggressive or disruptive or engage in delinquent behavior.
3. Their grades are falling.
4. They have lost interest in clubs, athletics, spending time with friends, or other activities they were formerly interested in.
5. They are compulsive partygoers, boy or girl chasers, thrill seekers, or daredevils. Or they may by just the opposite: They can never take a break and relax. They may be compulsive exercisers or may even study excessively.
6. They have low self-esteem.
7. They have unrealistic concerns that they are unattractive or disliked by others *(Quinn, 1997)*.

## Psychomotor Symptoms of Depression

### * Gross Motor Activity:

Unipolar depressed patients may have increased gross motor activity, and exhibited a greater amount of activity between midnight and 7:00 A.M. and had a greater percentage of their total 24-hour activity during these nighttime hours. While bipolar patients have decreased gross motor activity in their depressed state than in their euthymic and manic states. These changes were

found to occur during daytime but not nighttime hours *(Sobin and Sackeim, 1997)*.

*** Movements of the Head, and Limbs:**

The depressed patients were found to differ from the normal comparison group in the duration and frequency of selftouching (increased), direct eye contact with the interviewer (decreased), smiling (decreased), and eyebrow movement (decreased). These findings suggest that motor retardation and agitation are likely to be multidimensionally manifested *(Sobin and Sackeim, 1997)*.

*** Speech:**

The depressed patients may show slowed responses, monotonic phrases, poor articulation and paucity of speech. They may also have increased speech pause time (amount of time between utterance) during an automatic counting task. Also depressed patients had a reduced rate of change and less variability in mean vocal pitch when compared to a group of normal subjects *(Sobin and Sackeim, 1997)*.

*** Motor speed:**

Decision time (the time between stimulus presentation and release of the home key), motor response time (the time required to reach the decision key), and total reaction time were found to be slower in the related depressed group and improved after pharmachologic treatment of depression and subsequent symptom remission *(Ghozlan and Widlocher, 1989)*.

*** Characteristics of psychomotor symptoms:**

The variability of circadian peaks and lows was found to be increased in depressed patients as compared to normal subjects and this explains why the afternoon performance of the melancholic patients improved. In addition, both sex and age may be determinant of the manifestation of psychomotor symptoms. Males have more retardation than females, while females have more agitation than males. As regard age, depressed patients

under 40 years are more likely to have motor retardation, while over 40 are more likely to have motor agitation. Also depressed severity affect psychomotor manifestation, mouse with motor retardation were more likely to be psychotic than were those with motor agitation. This may indirectly suggest that global severity is associated with motor retarded but not motor agitated depression *(Sobin and Sackeim, 1997)*.

Motor retardation may predict superior response, and agitation may predict poorer response to some types of antidepressant medication, but the prognostic value of these symptoms with regard to ECT is uncertain *(Sobin and Sackeim, 1997)*.

***Simon et al, (1999)*** identified three different definitions of somatization used in earlier investigation. The first emphasizes presentation with somatic symptoms. ***Goldberge and Bridges (1988)*** point out that many patients with psychiatric disorders seek care for somatic symptoms. According to this definition patients with somatization are those who have psychiatric disorders but who present with somatic symptoms. The second definition emphasizes the association between depression and medically unexplained somatic symptoms *(Kroenke et al., 1994)*.

***Barsky (1992)*** describes the influence of psychological distress on the perception or reporting of somatic symptoms as "somatosensory amplification". According to this view, patients with somatization are those who have psychological disorders but who report multiple unexplained somatic symptoms. The third definition emphasizes the denial of psychological distress and the substitution of somatic symptoms. From this perspective, somatization is a psychological defense against the awareness or expression of psychological distress. *(Simon et al., 1999)*.

***Simon et al. (1999)*** findings suggest that somatic symptoms are a core component of the depressive syndrome, and that 60% of patients with major depression presented with somatic symptoms but acknowledged psychological symptoms (such as depressed mood or guilt) when specifically asked about

them. Patients may believe that the reporting of somatic symptoms is a more appropriate route for seeking help from a primary care physician.

***Goldberg and Bridges (1988)*** have called this process "facultative somatization" and have characterized the initial reporting of somatic symptoms as "a ticket for admission" to the primary care clinic. Thus, without specific questioning, depression and other psychological disorders may not be recognized.

There is substantial variation in how frequently patients with depression present with strictly somatic symptoms. In part this variation may reflect characteristics of physicians and health care systems, as well as cultural differences among patients ***(Simon et al., 1999)***.

## Suicide

In the United states, suicide is the fourth leading cause of death among children between the ages of 10 and 15 and the third leading cause of death among youth between the ages of 15 and 25 ***(CDC, 1995)***. Suicide rates among youth have been increasing steadily for the past four decades. This has led us to both report suicides in this age group and redouble our efforts to understand and address suicide among children ***(Potter et al., 1998)***.

***Apter et al. (1995)*** found two types of suicidal behavior in hospitalized adolescents: Internalizing type, associated with severe depression and apparent in youngster with MDD, or anorexia nervosa, and externalizing type, manifested by increased violence and appearing primarily in youngsters with conduct disorder, i.e., high levels of both depression and aggression.

***Stein et al. (1998)***: suggest that in patients already severely depressed and anxious, a high level of aggression would be the parameter that significantly predicts recidivism in suicidal adolescents.

Mood disorder has been identified as the single most predictive risk factor for adolescent suicide and the association

between major depression and adolescent suicide is even stronger than is generally indicated by data obtained in psychological autopsy studies *(Velting et al., 1998)*.

* **Association of serum cholesterol with major depression and suicide:**

Depression tends to result in a declining serum total cholesterol level, that was related to the subsequent risk of hospitalisation due to major depression and to death from suicide. Higher baseline serum high density lipoprotein (HDL) cholesterol was also associated with the risk of death from suicide *(Partonen et al., 1999)*.

* **Why there is lower rate of suicide in early compared with late adolescence?**

The four general explanations can be suggested : First: Less stress: Children are less exposed than adolescents to preciptants and risk factors that influence suicidal behavior. Thus intoxication and romantic failure both seem to contribute to adolescent suicide but not to younger's suicide. Second: More resilience: Children are equally exposed to these risk factors, but they have a higher threshold before these factors lead to suicide *(Aro et al., 1993)*. However *Groholt et al., (1998)* findings suggest that children and young adolescents are just as liable as older adolescents to commit suicide when exposed to the risk factors however those younger than 15 years are less exposed to risk factors, and for this reason have a lower suicide rate than those above 15years. Third : Immaturity: The planning and acting out of a suicidal act may require a level of maturity not yet reached by children and young adolescents. On the other hand, children may be unaware of the lethal risk connected with certain experimental or playful acts, leading to unintentional deaths being registered as suicides. Unlike those younger than 15 years, older adolescents in Norway are often familiar with the use of firearms and they are exposed to alcohol in social contexts. The same period is also characterized by biological changes and emerging sexual drives, which require new coping skills *(Groholt et al., 1998)*.

Fourth: Psychiatric disorders are found in more than 90% of adolescents committing suicide, with affective disorders representing the highest risk factor ***(Groholt et al., 1998)***.

***Brent et al., (1999)*** results explained two possible factors:

First, the relationship between psychopathology and suicide may be moderated by cognitive development, with increasing cognitive maturity making the completion of suicide more likely. So that among younger adolescent suicide victims, there is an overrepresentation of cognitively precocious youths who may have been better able than their more immature peers to plan and excute a lethal suicide attempt.

Second, the main difference in overall rates of psychopathology between older and younger suicides was due to the greater prevalence of substance abuse in the older victims as noted by others ***(Groholt et al., 1998; Shaffer et al., 1996)***. Consequently, older victims were much more likely to be alcohol toxicology positive, with an increased risk for suicide using firearms ***(Brent et al., 1993)***. ***Gould et al. (1996)*** recently noted the critical role of alcohol abuse in increasing the likehood that an ideator may make an actual attempt.

**Why there is higher suicide rate among males?**

Because of higher suicidal intent, use of more violent methods, higher prevalence rates of conduct antisocial disorder and substance abuse, and greater vulnerability to stressors such as legal difficulties, financial problems, or interpersonal loss ***(Gould et al., 1996; Shaffer et al., 1996)***. Also the co-occurrence of mood, substance abuse and disruptive disorders is uniquely high in older male adolescents, for whom the highest adolescent suicide rates are observed ***(Shaffer et al., 1996)***. The greater tendency of males to be intoxicated during the suicide, and the greater risk to males associated with coming from a nonintact family ***(Brent et al., 1999)***.

# Other types of depression

## I- Subclinical depression:

*Murphy et al., (1989)* in a 16 year follow up study in Canada reported subjects with prodromal symptoms at baseline were approximately three times more likely to be incident cases than were subjects who were asymptomatic at baseline and that depressive symptoms not meeting criteria for major depression were among the single most important predictors of first onset MDD 1year later.

## II- Brief depression

There is a sizable number of cases who complain of marked anxiety and depression that lasts only briefly, and were associated with suicide attempts in some cases ***(Montgomery, 1990)***.

In Switzerland 10% of the population suffered from at least one episode of brief depression during a year and half. 5% had recurrences with at least 12 episode of brief depression during the year, All of them had suffered from occupational or social impairment ***(Angst and Dobler-Mikola, 1985)***.

**How can patients with three day depression be recognized?**

The female to male ratio is nearly two to one similar to that reported with major depression. They complain of depression, irritability and anxiety with accompanying loss of energy, poor concentration, poor appetite and sleep loss. They also describe marked feelings of pessimism, common and urgent suicidal thoughts, and impulsiveness and seem more prone to attempt suicide than do those with more conventional depression. The ability to work is impaired not only because the episodes are severe but also because of the frequency of their recurrence. The attacks have sudden onset and are not precipitated by precipitating adverse life events. During the episodes the sufferers have a tense, explosive quality with a hostility to those around them, which makes difficulties with relationships ***(Montgomery, 1990)***.

## III- Atypical Depression:

The presence of mood reactivity (partial to full mood improvement to positive environmental events) during the depressive episode, along with at least two of four associated features: Hypersomnia, hyperphagia, leaden paralysis, and rejection sensitivity (sensitivity to rejection by others) ***(Williamson et al., (2000)***.

***DSM-IV (1994)*** has included Atypical depression as a subtype for the mood disorder.

***Asnis et al., (1995)*** deduced that 29% of patients with a research diagnostic criteria diagnosis of depressive disorder met criteria for atypical depression. There was a significantly greater proportion of women (87.9%) among patients with atypical depression than among patients with nonatypical depression (61.7%). 15.5% depressed children and adolescents have atypical depression ***(Williamson et al., 2000)***. Patients with atypical depression had a significantly longer duration of current illness than patients with nonatypical depression, suggesting that patients with atypical depression have a more chronic illness ***(Asnis et al., 1995)***.

Atypical depression patients have a less severe biological dysfunction than those with a more endogenous or melancholic depression. The finding of a significantly higher cortisol response to intra muscular desipramine (which at low doses is a relative selective norepinephrine reuptake inhibitor ($\alpha 1$) and reliably stimulates the release of cortisol with minimal behavioral side effects) in patients with atypical depression suggesting that this group may have a less dysfunctional noradrenergic system than patients with nonatypical depression ***(Asnis et al, 1995)***.

## Treatment of depression

1- Psychotherapy

2- Pharmacotherapy

3- Prevention

### 1- Psychotherapy:

It includes:

- Cognitive behavioral therapy (CBT).
- Non directive supportive therapy (NST).
- Systemic behavioral family therapy (SBFT).

***Clarke et al. (1992)*** reported that greater severity of depression, state anxiety, and cognitive distortion at intake, each predicted a poor response to group cognitive-behavior therapy (CBT) in adolescent depressives.

***Jayson et al., (1998)*** found that greater depressive severity and late age at presentation predicted poor outcome in depressed adolescents treated with individual CBT.

Also earlier age at onset, comorbid dysthymia, anxiety or substance abuse, parent- child discord, parental divorce, and parental depression have all been related to prolonged depressive episodes and poorer child outcome ***(Sanford et al, 1995; Goodyer et al., 1997; Brent et al, 1998)***.

***Brent et al., (1998)*** deduced that major depression at the end of treatment was predicted by clinical referral source (versus referral via advertisement).

***Stark and his colleagues (1996)*** outlined a multifaceted intervention program for depressed children that spans at least 30 sessions and includes individual child and parent treatment, as well as family and school interventions. These investigators propose cognitive and behavioral techniques to help the child and

parents with the child's mood and social skills problems, parent's discipline, marital conflict and interpersonal negotiation strategies, and individual and family problem- solving and communications.

Parent involvement would seem to be an important component to add to the interventions, especially with younger children. Parental psychopathology and marital difficulties may be significant obstacles to successful treatment of the child unless addressed in some fashion. However getting parents to participate, cooperate, and preserve over an extended period is potentially very difficult, and family interventions vary greatly in parent acceptance, efficacy, and success with children of different ages. ***Brent and colleagues (1997)*** included a family treatment, but they found that many families refused it, and overall the results were inferior to those of cognitive- behavioral therapy (CBT) for depressed adolescents. ***Brent et al., (1997)*** also attempted to get depressed parents into treatment in their psychotherapy study, but few availed themselves of the opportunity. Thus considerable work is needed to develop treatments that can deal effectively with the problematic family context. Moreover, it goes without saying that extended and multi-focused treatment is also cost. ***Clarke et al., (1999)*** deduced that parent involvement in CBT was not associated with significantly enhanced improvement. These results are contrary to widely held clinical beliefs regarding the importance of involving parents in any child or adolescent treatment.

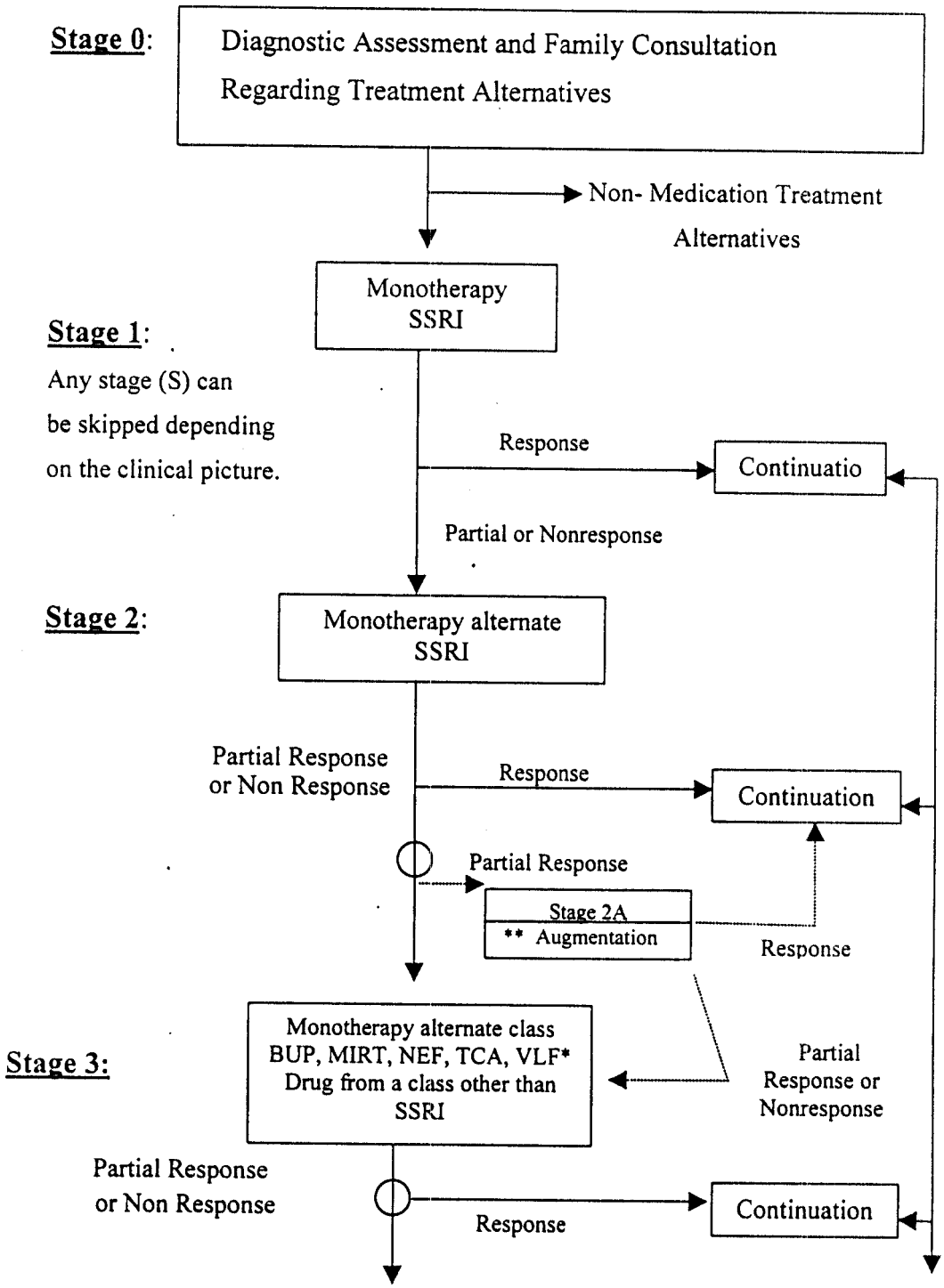
***Clarke et al., (1999)*** found that the 2-year recurrence rates of adolescent group with major depression or dysthymia (N=123) treated with CBT (16 two- hour sessions) then 24- month follow up period:

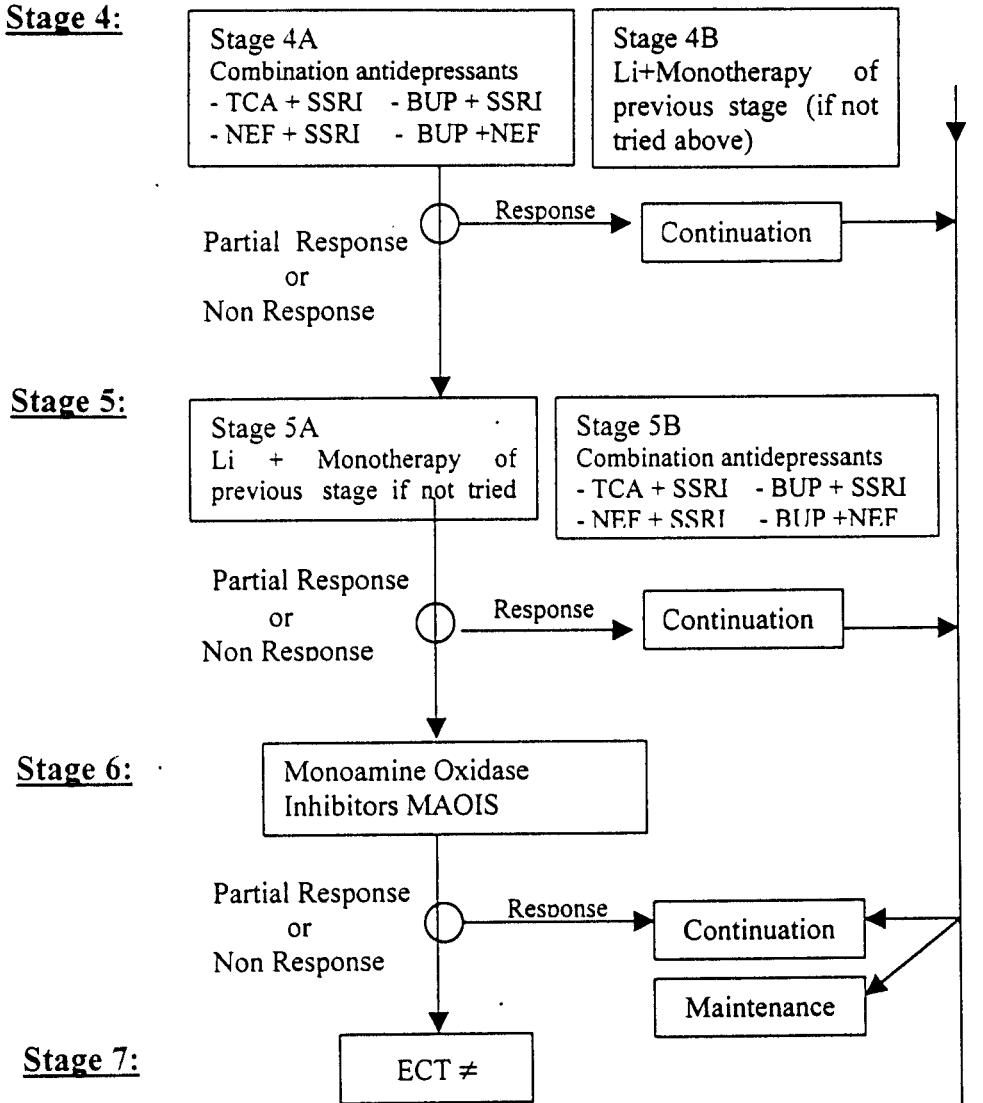
Assessment every 4 months or 12 month with booster sessions was 25% which is half the recurrence rates (50%) in treated adults ***(Belsher and Costello, 1988)***. This lower adolescent recurrence rate may be a function of treating individuals earlier in life, before multiple depressive episodes

have generated substantial depressive scarring with its associated higher recurrence risk. Alternatively, it may be that their participants were not as severely depressed as the typical research sample of depressed adults and thus were not as likely to experience future depression recurrence *(Clarke et al., 1999)*.

## 2- Pharmacotherapy

### Childhood Depression Medication Algorithm






* Consider TCA / VLF
** Lithium buspirone
\+ Most studied combiation in adults
≠ ECT not allowed in Texas ≤ 16 years

SSRI = Selective serotonin reuptake inhibitor

BUP = Bupropion ; MIRT = Mirtazapine

NEF = Nefazodone ; TCA = Tricyclic antidepressant

VLF = Venlafaxine ; ECT = Electroconvulsive therapy

**Fig 1 : Medication algorithm for treating children and adolescents who meet DSM – IV criteria for major depressive disorder. Adapted from *Crisomon et al, (1999)***

**Table (4): Tactics for acute-phase treatment of Major Depressive Disorder: Within each pharmacotherapeutic strategy stage, approaches to conducting a therapeutic trial with an antidepressant**

| Assessment point | Clinical status | Plan[a] |
|---|---|---|
| Weeks 1-3 (Critical point 1) | Symptomatic | * Initiate medicine : adjust dose to lower end of therapeutic dose range or serum level if useful<br>* If patient shows rapid remission in first 2-3 weeks, this may be a placebo response; continue to offer treatment and encouragement. |
| Week 4 (Critical point 2) | *Response or remission.<br>* partial response[b] | * Go to continuation phase<br>* Satisfactory rate of improvement : observe.<br>* Rate too slow, tolerating well : increase dose. |
| | * Minimal or no. response patient intolerant of lowest therapeutic dose. | * Discontinue; proceed to next stage. |
| | * Minimal or no response; patient tolerating medicine | * Increase dose[c] |
| Week 6 (Critical point 3) | *Response or remission<br>* Partial response | * Go to continuation phase<br>* Satisfactory rate of improvement if previously increased dose: observe.<br>* Rate too slow, tolerating well: increase dose; if dose already increased to maximum consider augmentation stage 2 and after. |
| | *Minimal response, patient intolerant of higher dose | * Discontinue, proceed to next stage. |
| | *Minimal response, patient tolerant | *Augment with lithium or alternative augmenting agent if previous nonresponse with lithium augmentation. |

Table (4): Tactics for acute-phase treatment of Major Depressive Disorder (cont)

| Assessment point | Clinical status | Plan |
|---|---|---|
| Week 8<br>(Critical point 4) | *Response or remission | * Go to continuation phase |
| | *Partial response | * If tolerating regimen, augment with lithium (or alternative as above) if not prev. done at stage 2 and after.<br>* If not tolerating regimen go to next stage. |
| | *Minimal response to lithium augmentation for 2-3 weeks | * Discontinue; switch to next level in plan. |
| Week10<br>(Critical point 5) | *Response or remission | * Go to continuation phase |
| | * Partial response | * Increase lithium dose if not previously done at stage 2 and after<br>* If on higher lithium dose, go to next stage. |
| | *No or minimal response | * Go to next stage |
| Week 12<br>(Critical point 6) | *Response or remission | * Go to continuation phase |
| | *Response partial responder | * Go to next stage. |

a) For patients showing minimal or no response, total trial should not exceed 4 to 8 weeks. For patients with a partial response, the trial may last up to 12 weeks. Decisions to increase the dose or augment with lithium may be reasonably postponed at each critical point if the patient appears to be improving.

b) With partial response, the clinician and patient assess both the absolute degree of improvement and the rate of improvement. No or minimal improvement is less than 25% improvement in overall symptoms, partial response is between 25% and 49% improvement in symptoms, and response is ≥ 50% improvement.

c) In patients with psychotic depression, the clinician should assess whether to increase the dose of the antidepressant, the antipsychotic, or both ***(Hughes, et al., 1999).***

**Approach for MDD with Psychotic Features:**

It is approached in the same manner as nonpsychotic MDD, with the addition of an antipsychotic medication of the newer atypical ones because of the lower risk of side effects ***(Weinberg et al., 1998)***.

It is important in the assessment phase to evaluate the possible role of substance abuse as part of the diagnosis, and if there is no response by the end of stage 3, to evaluate further for possible bipolar disorder ***(Hughes, et al., 1999)***.

Alternatively, the physician may choose to use an antipsychotic alone on initial treatment with the addition of an antidepressant if improvement is not seen ***(Hughes et al., 1999)***.

**Guidelines for choosing Medication Versus Psychotherapy:**

* Severity.
* Other family member's response.
* Recurrent depression.
* Chronic depression.
* Has not responded to psychotherapy.
* Convenience for family.
* Psychosocial stressors.

***(Hughes et al., 1999)***.

## Treatment of brief depression:

* Neuroleptics in low doses.
* Lithium.
* Monoamine oxidase inhibitors.
* Psychotherapy: the patients need support and kindness, preferably of an unthreatening, unemotional kind ***(Montgomery, 1990)***.

## Treatment of atypical depression:

All tricyclic antidepressants other than clomipramine have been shown to predominantly block the reuptake of norepinephrine in contrast to serotonin *(Schatzberg, 1992)*. Thus patients with atypical depression, with a less dysfunctional noradrenergic system, would be expected to derive less benefit from treatment with tricyclic antidepressants than patients with nonatypical depression *(Schatzberg, 1992)*.

Atypical depression has repeatedly been shown to respond well to treatment with MAOIS which appear to predominantly affect serotonin in a number of brain regions *(Asnis et al, 1995)*.

### A. Tricyclic Antidepressants (TCAs):

Psychopharmacologic studies of various tricyclic antidepressants have not demonstrated a response rate significantly greater than placebo in childhood or adolescent depression *(Ryan et al., 1992; Kutcher and Matron, 1994 and Birmaher et al., 1996$_{a,b}$)* Although a report by *Sallee et al., (1997)* on intravenous clomipromine (CMI) for depressed adolescents found a significantly better response among active versus placebo subjects, this is experimental until the issue of cardiovascular safety of tricyclic antidepressants (TCAs) is more clearly delineated.

The relative failure of TCAs with juvenile depression led some to raise the possibility that delayed maturation of noradrenergic system may preclude adequate response to TCAs in younger populations. Others have speculated that more efficient deamination of tertiary compounds to more noradrenergic metabolites in juvenile patients, and effects of high levels of gonadal steroids on end-organ receptor sensitivity, may diminish response to TCAs in juvenile patients *(Birmaher et al., 1996$_b$)*. Other speculations have included sample characteristics (e.g. severe, chronic), difficulty of subtyping by future bipolar course, and high comorbidity *(Geller et al., 1992)*.

In addition the high rate of placebo response, even after a lead in placebo period, remains unexplained *(Birmaher et al., 1998)*.

**Side Effects of TCAs:**

TCAs lower the seizure threshold, have anticholinergic and hypotensive effects, affect cardiac conduction, are dangerous in overdose, and may cause weight gain. There have been a number of case reports of sudden unexplained death occurring in children stable on TCA medications *(Varley and Mcclellan, 1997)*.

The potential association of TCAs with sudden death remains unknown. Reports of long-term maintenance have documented some electrocardiographic changes not present at short –term treatment, which suggest that periodic monitoring is required *(Leonard et al., 1995)*.

Heart rate variability (i.e. the change in beat –to- beat rate) is higher in children than in adults. Desipramine (DMI) significantly reduced heart rate variability *(Mezzacappa et al., 1998)*.

At present, TCAs are not considered first-line medications for child psychiatric disorders. The questions of using them if other drugs are not helpful is controversial because of the unresolved issue of possible sudden unexplained cardiac fatalities. If clinicians do prescribe TCAs, it is important to be that families are fully informed of potential cardiovascular complication *(Geller et al., 1999)*.

**Nontricyclic Antidepressants in children and adolescents**

*** Selective serotonin reuptake inhibitors (SSRIs)**

Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, Citalopram SSRIs may be particularly useful for the management of young patients with either depression or obsessive compulsive disorder (OCD) because their safety profiles are superior to those of tricyclic antidepressants and do not require the therapeutic drug monitoring recommended for TCAs *(Preskson, 1993)*.

The data support the effectiveness of SSRIs in the short term treatment of relatively severe persistent MDD in children and adolescents *(Emslie et al, 1999)*.

Depressed patients treated with a SSRI for at least 120 days experienced the lowest risk of relapse (re-emergence of original symptoms) and recurrence (a new episode) of depression *(Claxton et al., 2000)*.

*** Sertraline:**

It is a SSRI that has been used effectively in the dose range of 50-200 mg/d for treatment of depression and obsessive compulsive disorder. It is safe and likely to be effective in the treatment of pediatric patients with either major depression or OCD. There were no differences in the frequencies of adverse events between children and adults, other than higher incidence of dyspepsia among patients 6 to 12 years old *(Alderman et al., 1998)*.

Sertraline is non sedating and impairs neither psychomotor nor cognitive performance. However, it did not improve bodily complaints which are very frequent in the Egyptian depressives *(Gawad and Osman, 1991)*.

*** Side effects of Sertraline:**

- Autonomic nervous system, the most common are: Dry mouth, blurred vision, nausea, constipation, excessive sweating, and abdominal colics.
- Adverse behavior side effects were: Mainly drowsiness, less common are insomnia and nervousness.
- Miscellaneous side effects: Mainly headache, light-headedness, dysuria, loss of appetite, repeated yawning, sense of teeth clenching and numbness in the face. However, the discomfort caused by these side effects are tolerable and rarely led to discontinuation of therapy. *(Alderman et al., 1998)*.

Compliance is less likely to be a problem with sertaline, since the distressing side effects are minimal and well tolerated

and the drug is administered in one single dose per day *(Gawad and Osman, 1991)*.

There is lower incidence of dry mouth, somnolence, constipation, blurred vision, postural dizziness, and confusion than amitriptyline and desipramine *(Dogan, 1991)*. *Alderman et al., (1998)* found that the incidence of adverse events was not significantly correlated with any pharmacokinetic parameter, any demographic characteristic, or the dose titration schedule used to reach the final 200 mg/d dose.

**Non SSRIs:**

**Venlafaxine (Effexor):**

It is one of the new antidepressants which acts by inhibition of norepinephrine and serotonin reuptake, and unlike tricyclic antidepressants, it has no significant affinity for muscarinic, $\alpha_1$ adrenergic or histaminergic receptors, and does not inhibit monoamine oxidase. So it is more tolerable than tricyclic antidepressants and monoamine oxidase inhibitors *(Jonathan et al., 1996)*.

Venlafaxine showed some evidence of superiority to paroxtine in patients failing to respond to initial antidepressant therapy *(Poirier and Boyer, 1999)*.

*Mandoki et al., (1997)* found a significant improvement in children and adolescents in the MDD treated with venlafaxine but could not attribute improvement to venlafaxine drug therapy. Low dosage and Short length of treatment may account for the lack of efficacy. The findings did however suggest a low side-effect profile.

Further studies are recommended to assess efficacy and to collaborate its safety in children and adolescents.

*** Nefazodone:**

Recently *Wilens et al., (1997)* reported that 4/7 (56%) children with treatment refractory depression were much or very much improved on nefazodone. The antidepressant activity of

nefazodone is presumed to be linked to the potentiation of serotonergic activity. Nefazodone works at both sites of the serotonin receptors. It blocks the 5 HT2 receptor (Postsynaptic) and inhibits serotonin reuptake (Presynaptic). It has no significant affinity for $\alpha_2$ adrenergic, β-adrenergic, domapinergic, or cholinergic receptors and has weak $\alpha_1$ adrenergic blocking activity ***(Emslie et al., 1999)***.

*** Monamine oxidase inhibitors (MAOIS) :**

They have been rarely used with children to avoid the risk of hypertensive crisis associated with the intake of food or drugs containing tyramine during MAOI treatment ***(Mccabe, 1986)***.

Recent studies with new MAOI agents which are devoided of the risk of hypertensive crisis and include selective MAOIs type B ***(Sunderlant et al., 1985)*** or reversible MAOIs ***(Hilton et al., 1995)***. The development of safer compounds permits consideration of MAOIs for treatment in children.

**MAOI: Irreversible**

* Phenelzine (Nardil : Most commonly prescribed MAOI in the U.S. Also regularly prescribed throughout foreign markets (i.e. Canada and Europe) for depression.
* Tranylcypromine (Parnate) : Most centrally stimulating of MAOIs. Like phenelzine, tranylcypromine is prescribed more often in foreign markets than in the U.S.

**MAOI-A : Reversible (selective for monamine oxidase A):**

* Moclobemide: Available in foreign morkets for the treatment of depression, and to a lesser degree, social phobia. It is thought to have greater therapeutic flexibility than the other R-MAOIs-A, that have been marketed.
* Brofaromine: Like Moclobemide, it is used as an antidepressant and an anxiolytic in foreign markets.
* Toloxatone: Is available in France as an antidepressant.

* Defloxatone: The most likely R-MAOI-A to be approved in the U.S. because of its improved pharmacokinetics (i.e. longer half- life) over similar R-MAOIs-A.

* R-MAOIs-A in various stages of development world wide include Cimoxatone, Pyrazidole, Incazane, and Amiflamine.

**MAOI-A:Irreversible(Selective for monoamine oxidase A):**

* Clorgyline : Research as an antidepressant has been abandoned. It is useful as an experimental agent.

**MAOI-B:Irreversible(Selective for monoamine oxidase B):**

* Selegiline (deprenyl): Used in the U.S. for the treatment of parkinson disease. It has been reported to be a useful antidepressant, particularly in the elderly.

* Pargyline (Eutron) (Predominantly a MAO- Binhibitor at low doses): A number of studies have described its efficacy in treating attention deficit /hyperactivity disorder (as well as hypertension)

***(Emslie et al., 1999).***

***Ryan et al., (1988)*** reported data on the efficacy of irreversible mixed MAOIs from a chart review of 23 depressed adolescents, 21 of them treatment- resistant to heterocyclic antidepressants. Treatment with MAOIs alone or in combination with heterocyclic antidepressants resulted in 70% rating "good" or "fair" response.

MAOIs inhibit the monoamine oxidase (MAO) enzymes, which prevents tyramine from being inactivated in the intestinal tract and potentiates by 30 to 40 fold the sensitivity of the peripheral noradrenergic neurotransmitters in nerve terminals leading to the production of hypertension by the ingestion of products containing tyramine. Because more than 75% of MAO enzymes contained in the digestive tract are type A ***(Youdim and Riederer, 1993)***, only those MAOI agents which block type A

enzyme can precipitate a hypertensive crisis. For this reason, new MAOI agents that do not carry the risk of hypertensive crisis such as reversible MAOI-A and selective MAOI-B are being developed, with rising tyramine levels, a reversible inhibitor would progressively be displaced from the active site of the enzyme (MAO) and later would again become able to deaminate the deleterious amine (tyramine) ***(Waldmeier, 1993)***.

**Lithium:**

In 2 uncontrolled studies, approximately 40% of youth inadequately responding to tricyclics showed a favorable response to the combination of tricyclics and lithium ***(Strober et al., 1992)***.

Common lithium side effects in children include nausea, diarrhea, tremor, enuresis, fatigue, ataxia ***(Silva et al., 1992)***, leukocytosis and malaise, less commonly seen are renal, ocular, thyroid, neurological, dermatological and cardiovascular effects. Changes in weight and growth, diabetes, and hair loss are also seen ***(Rosenberg et al., 1994)***. Children younger than age 6 may experience neurological effects relatively frequently ***(Hagino et al., 1995)***, and in general younger children seem to experience more side effects than do older children ***(Ryan et al., 1999)***.

**Electroconvulsive therapy (ECT):**

Texas, states do not permit ECT for patients younger than age 16 years. Nontheless, the consensus panel agreed that it is important to include it as a last- resort treatment option as it has been used with some success ***(Hughes et al., 1999)***.

**The side effects of ECT can be minimized as follows:**

To Minimize adverse cognitive effects associated with ECT include limiting the number and frequency of treatment (With twice weekly ECT), use of moderately suprathreshold brief pulse stimuli, unilateral electrode placement, and oxygenation ***(Prudic and Sackeim, 1996)***.

***Khan et al., (1994)*** reported a study of eight patients in whom 0.5mg thyrotrophin-releasing hormone was adminstered

5min after ECT which improved attention and verbal fluency but did not impact on tests of memory. ***Stern et al., (1995)*** reported significant differences in retrograde, but not anterograde memory testing for the liothyronine group of rat receiving electroconvulsive shock (ECS) compared with placebo group receiving ECS.

Seizure threshold or duration can be limited with the use of propofol (new anesthetic agent) ***(Prudic and Sackeim, 1996)***.

**Biochemistry and physiology of ECT:**

***Devanand et al., (1995)*** studied the behavior of plasma GABA (Gamma aminobuteric acid) in patients undergoing ECT. They found that it was reduced for about 1 hour after ECT, and that patients with the highest baseline level of GABA before and after ECT course were the most likely to respond to treatment.

Patients with abnormal EEG findings (mostly psychotically depressed pateints) had a poorer rate of response to unilateral ECT than patients with a normal EEG, but a strong response to bilateral ECT ***(Malaspina, et al., 1994)***.

## 3 - Prevention of depression:

Clinical trials have shown that the use of depression screening tests in primary care settings can increase clinician detection of depression which result in improved recognition and earlier treatment of depression with improved patient outcome ***(Kamerow, 2000)***.

Importance of early evaluation and treatment of depressed child first to avoid needless suffering of the child and the parents. Second depressive episodes in children last, on average, an entire school year, and the recurrence rate is high if the episode is not treated. Repeated bouts of depression may delay a child's intellectual psychological, and social development. Third depression in children, if not treated, is likely to be harder to treat

once the child grows into adolescence and adulthood *(Quinn, 1997)*.

Of even greater concern is that a fifth to a third of children diagnosed with depression will go on to develop a bipolar illness, and that the children most likely to have such as outcome had certain things in common:

Their depressions started very quickly. They felt fatigued and slowed down when depressed, and their family histories were loaded with relatives over three generations who had mood disorders. Psychotic depressions also predicted the development of bipolar illness *(Quinn, 1997)*.

**Prevention of suicide:**

Screening for psychopathology among adolescents may be a way to detect youths at risk for suicide. Substance abuse e.g. alcohol increase risk for suicide using fire-arms. Also substance abuse and mood disorder which in turn conveyed a 50-fold increased risk for suicide *(Brent et al., 1999)*.

Abused youths appear to be a very high risk group who may require specialized and multimodal treatment *(Brent et al., 1999)*.

The effective targeting of a handful of factors namely past attempt, psychopathology in the adolescent, parental psychopathology and gun in home is likely to result in a substantial reduction in the suicide rate among youth *(Brent, et al., 1999)*.

It is so important to enhance communication and close interpersonal relationships between parents and children and between children and their peers which may also result in positive physical and mental health outcomes *(Groholt et al., 1998)*.

Also reduction of gun access to teenagers in order to separate at risk youngsters from guns. This is very important specially in the united states where guns are more often used by

younger teenagers than they are in Norway ***(Chrisoffel et al., 1998)***.

***Brent et al., (1993)*** studies in the united states have indicated that guns increase the risk of teen suicide, with the increase directly related to the number of guns available and greatest for teenagers without known mental health risk for suicide.

The range of existing programs for prevention of youth suicide has been outlined in CDC's youth Suicide prevention programs: A Resource Guide suicide prevention efforts ***(CDC, 1995)*** were placed into the following categories: School gatekeeper programs, community gatekeeper programs, general suicide education, screening programs, peer support programs, crisis centers and hotlines, restriction of access to lethal means, and intervention after suicide.

## Prognosis of depression:

* Recovery from depression:
* Factors affecting recurrence of depression

### Recovery from depression:

One year after onset of MDD about 20% to 50% of children, adolescents, and adults with a major depression will not have recovered ***(Sargent, 1990)***. By 2 years the figure will be reduced from 8% to 10% ***(Warner, et al., 1992)***.

***Warner et al., (1992)*** also found differences in time to recovery from MDD in offspring by number of parental episodes of Major depression. They also found that recovery did not differ by age and sex of offspring but that an early age at onset predicted longer time to recovery. They also found that double depression, and impairment of social functioning did not affect recovery. Of the family risk factors only divorce was associated with an increased risk for a protracted time to recovery.

***Maj, (1994)*** confirmed the significance of duration and severity of the index episode, underlying dysthymia; premorbid neuroticism; family dysfunction; recent major life difficulties; and time to initial treatment as predictors of time to recovery from a depressive episode,

### Factors affecting recurrence of depression:

*** Impact of double depression:**

The high co-occurrence of dysthymia and MDD (double depression) in children has been shown to have a high morbidity, and were at increased risk for recurrence ***(Warner et al., 1992)***.

*** Social functioning:**

Impairment in social functioning was associated with increased risk of recurrence ***(Warner et al., 1992)***.

## *Chapter Two:*

# *Cytokines*

# CYTOKINES

It refers to a factor made by a cell (cyto) that acts on target cells. Cytokines are diverse group of intracellular signalling proteins that regulate not only local systemic and inflammatory responses against various agents and infections, but also wound healing, haematopoiesis and many other biological processes ***(Oppenheim et al., 1994)***. These biological activities are the result of functions they perform on the cellular level such as regulation of cell growth, proliferation, differentiation, mobility and metabolism of the cell ***(Mckenzie and Sauder, 1990)***. Cytokines act in either paracrine manner (on adjacent cell) or autocrine manner (on producing cell itself) or like true hormones at distant cell that is stimulated via cytokines that have been secreted into the circulation (endocrine action) ***(Abbas et al., 1999; Leonard, 1999)***.

Cytokines are peptides or glycoproteins with molecular weight (mw) ranging between 6-60 kilodaltons (kd) ***(Arai, 1990)***. Cytokines are secreted by all body cells and bind to specific receptors present on the surface membrane of their target cells, that are widely distributed all over the body ***(Lugar et al., 1990)***.

Cytokines possess pleotropic activities, that can affect different types of cells or can affect one type during various stages of its development. The presence of large number of cytokines with pleotropic effects lead to an overlap in biological effects between different cytokines ***(Oppenhein et al., 1994)***.

Cytokines often have multiple different effects on the same target cell. Cytokine actions are often redundant (i.e. many functions originally attributed to one cytokine have proved to be shared properties of several different cytokines) ***(Abbas et al., 1999)***.

The ability of one cytokine to enhance or suppress the production of others may provide important positive and negative regulatory mechanisms for immune and inflammatory responses.

A cytokine may augment the action of other cytokine, a kind of interaction known as synergy *(Abbas et al., 1999)*.

Cyokines share in the communication between the immune system and other organs. The immune system shares with the nervous system in their ability to signal via the hypothalamus pituitary adrenal axis, since several cytokines as IL-1, IL-6, and TNF have direct effect on the hypothalamus or pitutary gland. Cytokines released during immune responses regulate the growth, mobility and differentiation of lymphocytes. They might exert similar influence over other leukocytes and even non-white blood cells. They are neither antigen binding nor antigen specific *(Coleman et al, 1992)*.

Cytokine secretion is a brief, self-limited event. In general, cytokines are not stored as preformed molecules, and their synthesis is initiated by new gene transcription. Such transcriptional activation is usually transient, and the messenger ribonucleic acids (mRNAs) encoding cytokines are unstable. The combination of a short period of transcription and a short-lived mRNA transcript ensures that cytokine synthesis is transient *(Abbas et al., 1999)*.

## Physiology of cytokines:

### A) Production and synthesis :

Most cytokines are produced as a result of certain stimuli as cell injury, tumour promotors, bacterial products or parts of bacteria, viruses, substance-P, and ultraviolet irradiation. Furthermore some cytokines can induce the synthesis of themselves or of other cytokines. These stimuli act by binding to cell surface receptors *(Lugar et al., 1990)*.

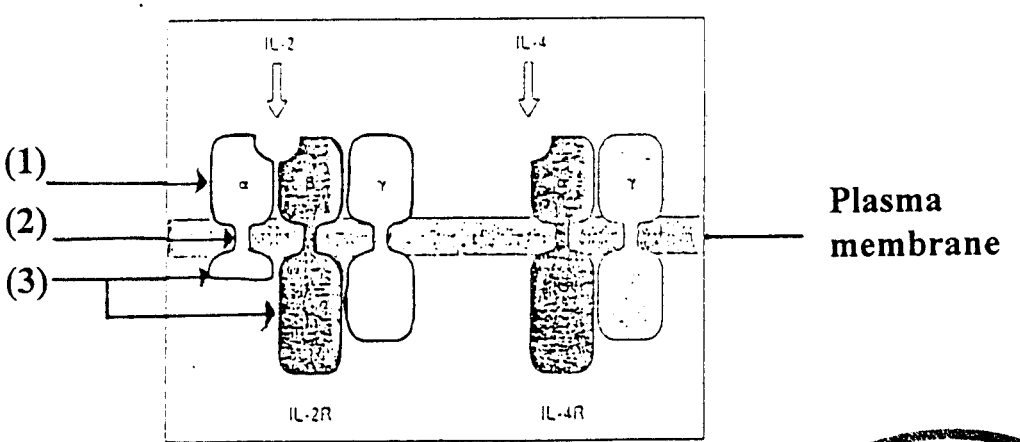
### B) Cytokine receptors and intracellular signal transduction :

Most cytokine receptors are high affinity receptors. Each cytokine interacts in a highly specific manner with its cell receptor. The general structure of cytokine receptor comprises three distinct domains *(Sugamura et al., 1995)* (Fig2).

1) The recognition domain : Protrudes outward from the plasma membrane and confirms specificity as regards to the binding of particular cytokine.

2) The second domain: Is hydrophobic. It spans the plasma membrane lipid bilayer from its outer to its inner surface and anchors the receptor to the plasma membrane.

3) The third domain: Is located on the inner surface of the plasma membrane and functions as signaling device to other molecules present in its vicinity.




(1) Extracellular (Recognition domain).

(2) Second domain.

(3) Intracellular domain.

**Fig (2) : General structure of Cytokine Receptor** ***(Sugamura et al., 1995).***

## Classification of Cytokines (Roitt et al., 1998):

1) **Interleukins:** There are now 18 interleukins which are proteins of polypeptides. They were defined as molecules made by leucocytes, to act on leucocytes. Although subsequent researches have revealed that some of these molecules are also made by non leucocytes and that may also act on non leucocytes, the nomenclature has stuck.

2) **Tumour Necrosis Factors Group :** It is structurally unrelated to IL-1 and binds to different cellular receptors. Yet their spectra of biologic effects overlap considerably.

3) **Interferons (IFNs)**: Have antiviral as well as regulatory and differentiation properties. IFNs are 2 subgroups:

   a) **Type I IFNs (IFN α and IFN β)** : IFNα is produced by leucocytes. IFN β is produced by fibroblasts. Type I subgroup has mainly antiviral properties.

   b) **Type II IFN (IFN γ)** Which is secreted which is secreted by $CD8^+$ cells and some $CD4^+$ cells. INFγ has a weak antiviral effect. It is considered mainly immune regulatory cytokine.

4) **Growth Factors:** Which are mainly involved in the differentiation and maturation of stem cells into different lineages in bone marrow. As macrophage-CSF, granulocyte-CSF, granulocyte macrophage-CSF.

5) **Chemokines:** Are low molecular weight peptides which are leucocyte attractants. They are secondary proinflammatory mediators that are induced by primary proinflammatory mediators such as IL-1 and TNF. They show high specificity i.e. each chemokine is produced by particular cells and acts as chemoattractant for specific cell type. Unlike classical leucocytes chemoattractants which have little specificity, chemokines have two subfamilies. The α subfamily which are chemoattractants for neutrophils and B subfamily which are chemoattractants for monocytes, basophils, eosinophils, and lymphocytes but not neutrophils.

*Table (5) Cytokines Classification*

| *Cytokine* | *Immune system source* | *Other cells* | *Principal targets* | *Principal effects* |
|---|---|---|---|---|
| **1- Interleukins:** | | | | |
| IL-1α<br>IL-1β | Macrophages,<br>LGLs, B cells | Endothelium, fibroblasts,<br>astrocytes, etc. | T cells, B cells,<br>macrophages endothelium,<br>tissue cells. | Lymphocyte activation, macrophage stimulation, ↑ leucocyte /endothelial adhesion, pyrexia, acute phase proteins |
| IL-2 | T cells | | T cells | T-cell proliferation and differentiation, activation of cytotoxic lymphocytes and macrophages. |
| IL-3 | T cells | Stem cells | | Multilineage colony stimulating factor |
| IL-4 | T cells | | B cells, T cells | B-cell growth factor, isotype selection, IgE, IgG1 |
| IL-5 | T cells | | B cells | B-cell growth and differentiation, IgA selection |
| IL-6 | T cells, B cells | Fibroblasts, macrophages | B cells, hepatocytes | B-cell differentiation, induces acute phase proteins |
| IL-7 | | Bone-marrow stromal cells | Pre-B cells, T cells | B-cell and T-cell proliferation |
| IL-8 | Monocytes | Fibroblasts | Neutrophils, basophils, T cells, keratinocytes | Chemotaxis, angiogenesis, superoxide release, granule release. |
| IL-9 | T cells | | | Enhances T-cell survival, mast cell activation, synergy with erythropoietin |
| IL-10 | T cells | | $TH_1$ cells | Inhibition of cytokine synthesis |
| IL-11 | | Bone marrow<br>Stromal cells | Haemopoietic progenitors<br>osteoclasts | Osteoclast formation, colony stimulating factor, elevates platelet count in vivo inhibits pro-inflammatory cytokine production |
| IL-12 | Monocytes | | T cells | Induction of $TH_1$ cells |
| IL-13 | Activated T cells | | Monocytes, B cells | B-cell growth and differentiation, inhibits pro-inflammatory cytokine production |
| IL-14 | T cells | | | Stimulates proliferation of activated B cells, inhibits Ig secretion |

*Table (5) (cont) Cytokines Classification*

| *Cytokine* | *Immune system source* | *Other cells* | *Principal targets* | *Principal effects* |
|---|---|---|---|---|
| IL-15 | Monocytes | Epithelium, muscle | T cells, activated B cells | Proliferation |
| IL-16 | Eosinophils, CD8+ T cells | | CD4+ T cells | Chemoattraction of CD4+ cells |
| IL-17 | CD4+ T lymphocytes | | Epithelium, fibroblasts, endothelium | Release of IL-6, IL-8, G-CSF, PGE2, enhances ICAM-1, stimulates fibroblasts to sustain CD34+ prgoenitors |
| IL-18 | | Hepatocytes | PBMC | Induces IFNγ production enhances NK activity |
| **2- Tumor necrosis Factors:** | | | | |
| TNFα | Macrophages, mast cells, lymphocytes | | Macrophages granulocytes tissue cells | Activation of macrophages, granulocytes and cytotoxic cells, leucocyte/endothelial cell adhesion, cachexia, pyrexia, induction of acute phase protein, stimulation of angiogenesis, enhanced MHC class 1 production |
| TNFβ (LT) | Lymphocytes | | | As for TNFα |
| **3- Interferons:** | | | | |
| IFNα | Leucocytes | Epithelia, fibroblasts | Tissue cells | MHC class 1 inducation, antiviral state, stimulation of NK cells, anti-proliferative, stimulates IL-12 production and $TH_1$ cells |
| IFNβ | | Fibroblasts, epithelia | Tissue cells, leucocytes | MHC class I induction, antiviral state, anti-proliferative. |
| INFγ | T cells, NK cells | Epithelia, fibroblasts | Leucocytes, tissue cells, $TH_2$ cells | MHC class I and II induction, macrophage activation, # endothelial cell/lymphocyte adhesion, MØ cytokine synthesis, antiviral state, anti-proliferative ($TH_1$ cells) |

*Table (5) (cont) Cytokines Classification*

| *Cytokine* | *Immune system source* | *Other cells* | *Principal targets* | *Principal effects* |
|---|---|---|---|---|
| **4- Growth Factors:** | | | | |
| M-CSF | Monocytes | Endothelium, fibroblasts | | Proliferation of macrophage precursors |
| G-CSF | Macrophages | Fibroblasts | Stem cells | Stimulates division and differentiation |
| GM-CSF | T cells, macrophages | Endothelium, fibroblasts | | Proliferation of granulocyte and macrophage precursors and activators |
| **5- Chemokines:** | | | | |
| MIF | T cells | | Macrophages | Migration inhibition |
| MCP-1 | Monocytes | Epithelia | Monocytes, T cells, mast cells, basophils, stem cells | Chemotaxis, adhesion, histamine release, inhibition of colony formation |
| MIP-1α | T cells, monocytes, neutrophils | Fibroblasts | Monocytes, T cells, B cells, NK cells, mast cells, eosinophils, dendritic cells, stem cells | Chemotaxis, adhesion inihibition of colony formation |
| RANTES | T cells | | Monocytes, T cells, NK cells, eosinophils, basophils, dendritic cells | Chemotaxis, histamine release |
| Eotaxin | Monocytes | | Eosinophils | Chemotaxis |
| IP-10 | Monocytes | | T cells, NK cells, endothelial cells | Chemotaxis, cytolytic activity, inhibition of angiogenesis |

IL: Interleukin, TNF = Tumor necrosis factor, IFN: Interferon, M-CSF: monocyte-colony stimulating factor, G-CSF: Granulocyte-CSF, GM-CSF: granulocyte monocyte-CSF, MIF: Macrophage migration inhibition factor, MCP-1: Monocyte chemotactic peptide-1, MIP: Macrophage inflammatory protein, RANTES: Regulated upon activation normally T cell expressed and secreted, IP-10: Inhibition protein number 10.

***(Roitt et al., 1998).***

## Another classification of cytokines and their receptors according to Leonard (1999):

## Type I Cytokines:

They are appropriately described as α-helical bundle cytokines because their three-dimensional structures contain four α-helices. The first two and last two of these α-helices are each connected by long-overhand loops. Type I cytokines can be grouped based on their size into.

a) Short-chain: It includes IL-2, IL-3, IL-4, IL-5, granulocyte macrophage colony stimulating factor (GM.CSF), IL-7, IL-9, IL-13, IL-15, monocyte-CSF (M-CSF), and stem cell factor (SCF).

b) Long-chain: It includes growth hormone, prolactin, erythropoietin, leptin, IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), and granulocyte-CSF (G-CSF).

### Receptors for Type I Cytokines:

They are generally type I membrane – spanning glycoproteins. They have

- **N-terminal extracellular domains:**

These include four conserved cysteine residues involved in intrachain disulfide bonds. In addition, a membrane proximal region WSXWS (trp-ser-x-trp-ser) motif was found to be generally conserved. Another shared feature of type I cytokine receptors is the presence of fibronectin type III domains.

- **C-terminal intracellular (Cytoplasmic) domain:**

A membrane-proximal region known as the Box-1/Box-2 region is conserved, with a proline rich Box1 region being the most conserved.

*N.B:* IL-2Rα is not a type I cytokine receptor as it has an extremely short cytoplasmic domain that does not appear to play a role in signaling. Also soluble receptor protein IL-2Rα is not a type I cytokine receptor, because it can be created by proteolytic cleavage of the membrane receptors (i.e. It is not a complete receptor, there is part of it missing). Soluble receptors could serve as cytokine carrier proteins and potentially could increase stability of a cytokine by protecting it from proteolysis ***(Fernandez-Botran et al., 1996)***.

**Type II cytokines (Interferons) and their receptors:**

- Type I interferons (IFNs): IFNα, IFNβ, IFNγ, $IFN_8$
- Type II interferons: IFNι
- IL-10

***(Leonard, 1999)***

## Cytokine Receptors Families

### 1. Immunoglobulin (Ig) Superfamily:

Common in platelet-derived growth factor or fibroblast growth factor receptors, and in receptors for certain colony-stimulating factors such as c-kit ligand and monocyte-colony stimulating factor (M-CSF).

### 2. Cytokine receptor family (Type I):

It involves a conserved extracellular sequence of five amino acid residues, tryptophan-serine-X-tryptophan-serine (written as WSXWS in the single letter amino acid code), where amino acid residue x is variable. This small motif is contained witin a larger conserved domain additionally characterized by two conserved cysteine residues. The prototypic molecule for this family was growth hormone, and this structure is shared by IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-13, IL-15, granulocyte, monocyte colony-stimulating factor

(GM-CSF) and (G-CSF). Interestingly, the IL-6 receptor contains both an Ig domain and the two cysteine/WSXWS motif.

**3. Cytokine receptor family (Type II):**

The type I and type II interferon (IFN) receptors.

**4. Type III cytokine receptors [Tumor necrosis factor (TNF) receptor] family:**

The structural motif identified in cytokine receptors is a cysteine-rich domain first identified in the two TNF receptors (TNF-R I and TNF-RII).

## 5. Seven Transmembrane Helix Family:

It is a very large family of molecules that includes the receptors for the chemokines, this motif (sequence homologies) was originally found in β-adrenergic receptors and retinal rhodopsin and is common to all receptors that are coupled to heterotrimeric guanosine triphosphate (GTP)-binding signalling proteins ***(Abbas et al., 1999)***.

## *Chapter Three:*

# *Interleukin-2*

# Interleukin-2 (IL-2)

IL-2 is an autocrine and paracrine growth factor that is secreted by activated T lymphocytes and is essential for clonal T cell proliferation. Its essential role in T cell proliferation, cytokine production, and on the functional properties of B cells, macrophages, and NK cells, places IL-2 among the most critical immunoregulatory cytokines *(Oppenheim et al, 1995)*.

IL-2 is a glycoprotein with molecular weight of 15.4 kd and 133 amino acid long arranged into 7- helices (A,B,B,C,D, E, and F) from the N-terminal. Destruction of the internal disulphide bond will destroy the biological activity of IL-2. The tertiary folded structure of IL-2 is obligatory for stimulating growth of T cells *(Waldman, 1993)*.

## Regulation of IL-2 production :

Resting T lymphocytes do not synthesize or secrete IL-2 protein but can be induced to do both by appropriate combinations of antigen and costimulatory factors, or by exposure to polyclonal mitogens. IL-2 production occurs mainly in CD4 helper T cells. However, CD8 lymphocytes and some NK cells also can be induced to secrete IL-2 under certain conditions *(Oppenheim et al., 1995)*.

IL-2 production can be inhibited or augmented by a variety of physiological and non physiological agents. IL-1 can enhance IL-2 production. Vasopressin and other neurohormons, hydroxyurea, phytohaemagglutinin and sodium-azide can enhance IL2 production. These compounds act by decreasing cellular proliferation, thus prolong G1 phase (active state). IL-2 production is inhibited by human suppressor T-cells, immunosuppressors such as steroids, cyclosporin, prostaglandin E2. Steroids and cyclosporin inhibit gene expression for IL-2 at the level of m RNA transcription, while prostagelandin E2 inhibits accessory cell functions *(Smith, 1988)*. IL-2 gene is located on chromosome 4q26-27/3 *(Leonard, 1999)*.

Hypoproduction of IL-2 occurs in diseases associated with cell mediated immune deficiency involving T lymphocyte function such as systemic lupus erythematosis, advanced metastatic cancer, AIDS, primary immunodeficiency. Meanwhile, cultured lymphocytes from synovial fluid of rheumatoid arthritis patients produce more IL-2 upon activation ***(Smith, 1988)***.

## Functions of IL-2:

### Effect of IL-2 on T cells :

Binding of IL-2 to its high affinity receptor either in paracrine or autocrine mode irritates clonal expansion of activated Tcells. On exposure to activating stimuli $CD4^+$ T lymphocytes begin to express both IL-2 and IL-2R and shortly thereafter start to proliferate. $CD8^+$ T cells are generally unable to produce adequate amount of IL-2 and so require exogenous IL-2 from helper cells to proliferate. Stimulated T cells by IL-2 exhibit enhanced cytotoxicity and produce lymphokines such as IFN $\gamma$, TNF $\beta$, TGF $\beta$, and $\beta$ cell growth factors such as IL-3 and IL-5 ***(Male et al, 1996)***.

### Effects of IL-2 on non T cells:

The NK cells are always IL-2 responsive. Unstimulated NK cells bind IL-2 with relatively low affinity and proliferate only in response to correspondingly higher IL-2 concentrations. Once stimulated by IL-2, they begin to express the IL-2R$\alpha$ chain and so acquire high affinity receptors. IL-2 stimulated NK cells have enhanced cytolytic activity and secrete numerous cytokines including IFN$\gamma$ and TNF$\alpha$ that are potent activators of macrophage. Also IL-2 induce lymphokine activated killer (LAK) activity which is predominantly due to NK cells ***(Male et al., 1996)***.

Activated or transformed $\beta$ lymphocytes express high affinity IL-2R at approximately 30% the density found on activated Tcells. IL-2 enhances proliferation and Ab secretion by

normal βcells. It also influences heavy chain class switch, biasing β cells towards expression of $IgG_2Ab$ ***(David et al., 1998)***.

Human monocyte and macrophages constitutively express low levels of IL-2R β chain but express high affinity receptors containing all the three chains on exposure to IL-2, IFNγ or other activating agents. Continued exposure of an activated macrophage to IL-2 enhances its microbicidal and cytotoxic activity and promotes secretion of hydrogen peroxide, TNFα and IL-6.Recent reports indicate that IL-2 can activate neutrophils as well ***(Theze el al., 1996)***.

***David et al, (1998)*** showed that IL-2R α is not expressed on the cell surface of lymphocytes, but it is expressed and stored as an intracellular component. These data indicate that peripheral blood mononuclear cells (PBMC) subsets involved in specific responses are spontaneously insensitive to IL-2 and that IL-2 responsiveness is acquired after antigenic challenge. By contrast, cells involved in inflammatory and tumoricidal processes are readily sensitive to IL-2 stimulation.

**New functions for the IL-2 system:**

IL-2 can suppress aptosis in cytotoxic T cells by a mechanism that involves the activation of protein kinase C ***(Theze et al., 1996)***.

It has been suggested that IL-2 plays a role in the establishment of an anergic state at the T cell level ***(Lu et al., 1994)***.

*Chapter Four:*

# *Interleukin-2 Receptors*

# Interleukin-2 Receptors
# (IL- 2R)

IL-2R is a specific cell surface receptor that mediates the effects of interleukin-2 (IL-2) on its target cells and plays a prominent role in the biology of T cells, B cells and NK cells during activation. It exists in vivo as a transmembrane complete molecule on cell surface and as a truncated soluble form in plasma (Junghans and Waldmann, 1996).

## Structure:

The IL-2R comprises three subunits encoded by different genes: Human IL-2Rα is located at chromosome 10 P14-15; IL-2R β is located at chromosome 22q and γc is located at xq13.1 (Leonard, 1999). The first one to be identifled is the IL-2R α, it is a polypeptide chain with a molecular weight of 55.000 and it has only 13 cytoplasmic amino acids. It binds IL-2 with low affinity and has no signaling activity. The IL-2 R α is the protein recognized by an antibody called anti-Tac which is widely used to detect IL-2R. It shares homology with the alpha chain of IL-15 receptor ***(Theze, 1994)***. IL-2R ά is the chain primarily responsible for the species specificity of IL-2 binding ***(Liu et al, 1996)***.

***Kobayashi et al. (1999)***, found that the soluble serum form of the alpha subunit of the IL-2 receptor (sIL-2Rα) (CD25, Tac) whose natural- life is approximately 40 min, survived much longer in the circulation when bound by a specific antibody. In addition, The same authors evaluated the extent to which sIL-2Rα protected IL-2 in freshly collected serum; as it protected IL-2 from forming complexes with α2- macroglobulin and from inactivation in vitro. In addition, the authors demonstrated that the anti-IL- 2Rα monoclonal antibody 7G7/B6, which does not inhibit the binding of IL-2 to its binding site on s IL-2Rα, protected IL-2 from degradation and inactivation in vivo in the presence of sIL- 2Rα. Thus the serum levels of IL-2 increased

more than 3 to 40 fold than those of groups receiving IL-2 alone, sIL-2 Rα or h Tac. Thus the use of antibodies against endogenous soluble receptors could increase the in vivo survival of cytokines, protect their bioactivity and thereby facilitate their clinical use in the treatment of various malignancies and AIDS ***(Kobayashi et al., 1999)***.

The importance of the α chain has been clearly demonstrated by the severely abnormal phenotype of IL-2Rα deficient mice, which exhibit autoimmunity, inflammatory bowel disease and premature death ***(Willerford et al., 1995)*** and more recently by recognition that IL-2Rα mutation can cause severe combined immuno deficiency (SCID) in humans ***(Sharfe et al., 1997)***. Although the α chain appears to lack a direct signaling function, it has a very fast "on" rate for IL-2 binding. Thus the combination of this rapid on rate with the slow off rate from IL-2R β/γc dimers results in high affinity binding that is vital for responding to the very low concentrations of IL-2 that are physiologically present in vivo. Moreover, because approximately 10 fold more low affinity than high affinity receptors are expressed on activated T cells, IL-2Rα may serve as an efficient means of recruitment and concentration of IL-2 on the cell surface, allowing more efficient formation of IL-2/IL-2R β/γc signaling complexes ***(Leonard, 1999)***.

The other two subunits identified are the IL-2Rβ and γ. The IL-2R β has a molecular weight of 75.000, and it has a large cytoplasmic domains of 286 amino acids. It plays a critical role in signal transduction. The IL- 2Rγ has a molecular weight of 64.000 and a cytoplasmic domains of 86 amino acids, it also participates in the formation of IL -4, IL-7, IL-9 and IL-15.

Consequently, defects in the IL-2Rγ expression affect several cytokines dependant systems and lead to severe immuno deficiency in humans ***(Male et al, 1996)***.

There are two functional types of IL-2R that are able to transmit growth signals expressed in humans: The intermediate –

affinity IL-2R expressed on resting T cells and it is formed by IL-Rβ plus IL-2Rγ, while the high-affinity IL-2R is a heterotrimer comprised of IL-2Rα, IL-2Rβ, IL-2R$\gamma_c$ subunit. Only activated T cells express high affinity receptors *(Eckenberg et al, 1997)*.

## Biological activity:

After cell activation, high affinity IL-2R is induced to maximal levels within 4-6 days. Expression then declines to undetectable levels by 6-10 days. The decline in receptor expression occurs regardless if IL-2 is present indicating that it is autonomously regulated. This ensures that within a few days after activation, the Tcell will become refractory to IL-2 and that clonal proliferation will cease. If such a cell is reactivated IL-2R reappears on the cell surface and IL-2 dependent proliferation will resume until the receptors disappear again 4-7days later. The transient nature of IL-2R expression helps to maintain the cyclical, self limiting pattern of normal Tcells growth in vivo *(Caruso et al, 1997)*.

## Interleukin 2 and IL-2R interaction:

Precise measurements of the binding affinities between IL-2 and the human IL-2R subunits confirmed that IL-2R α or β can bind directly IL-2, whereas IL 2Rγ alone has no measurable affinity for this cytokine *(Theze et al, 1996)*.

## Signaling through cytokine receptors:

The JAK-STAT pathway (Fig 3) is particularly exciting in that it serves as a rapid mechanism by which signals can be transduced from the membrane to the nucleus *(Leonard, 1999)*.

All receptors of the cytokine receptor superfamily, along with receptors from some of the other families are associated with molecules called the Janus Kinases (JAKs), Activation of cytokine receptors induce tyrosine phosphorylation and activation of JAKs, which is required for most if not all receptor functions. Box1 and Box2 of IL-2Rβ are responsible for binding of JAK1, whereas the equivalent region in IL-2Rγ binds $JAK_3$. JAK kinases

then couple ligand binding to tyrosine phosphorylation of various signaling proteins, including the signal transducers and activators of transcription (STATs). STAT dimers translocate to the nucleus and bind directly to DNA, and activate gene expression *(Rook and Balkwill, 1998; and Theze et al., 1996)*.

**Activation of the proto-oncogene (Ras) pathway:**

Ras is a 21-KD peripheral membrane protein and is one of many related proteins that can bind and hydrolyze guanine nucleoside triphosphate (GTP). Ras is activated in the GTP-bound state and is inactive in the GDP-bound state. The adaptor protein (Shc) has been reported to be inducibly tyrosine phasphorylated. Thus Shc activate Ras. Ras interacts directly with the serine threonine kinase Raf. Raf can regulate the activation of a dual-specific tyrosine-serine threonine kinase (MEK), that in turn activates mitogen-activated protein kinases (MAPKs). The activation of Ras contributes to the transcriptional activation of the IL-2 gene (which is located on chromosome 4), and cell proliferation *(Weiss, 1999)*.

**Inhibitors of cytokine signaling:**

There are two different classes of negative regulators of cytokine signaling. The first family includes: Suppressor of cytokine signaling (SOCS), JAK-binding protein (JAB), STAT-induced STAT inhibitor (SSI), and cytokine-inducible Src homology 2 domain (SM2)-containing protein (CIS). There are currently eight members, which share common structural elements. These proteins are able to bind to JAKs and inhibit kinase activity. As these proteins are induced by cytokines and function to inhibit cytokine signaling, this strongly suggest a model of classical negative feedback regulation. The second family of proteins are protein inhibitor of activated STAT (PIAS, PIAS3). The PIAS proteins inhibit DNA binding and transcriptional activation by their respective STAT parteners. Their domain appear to exert their function by blocking STAT tyrosine phosphorylation or by effecting the protein stability of STATs *(Chen et al., 1998)*.

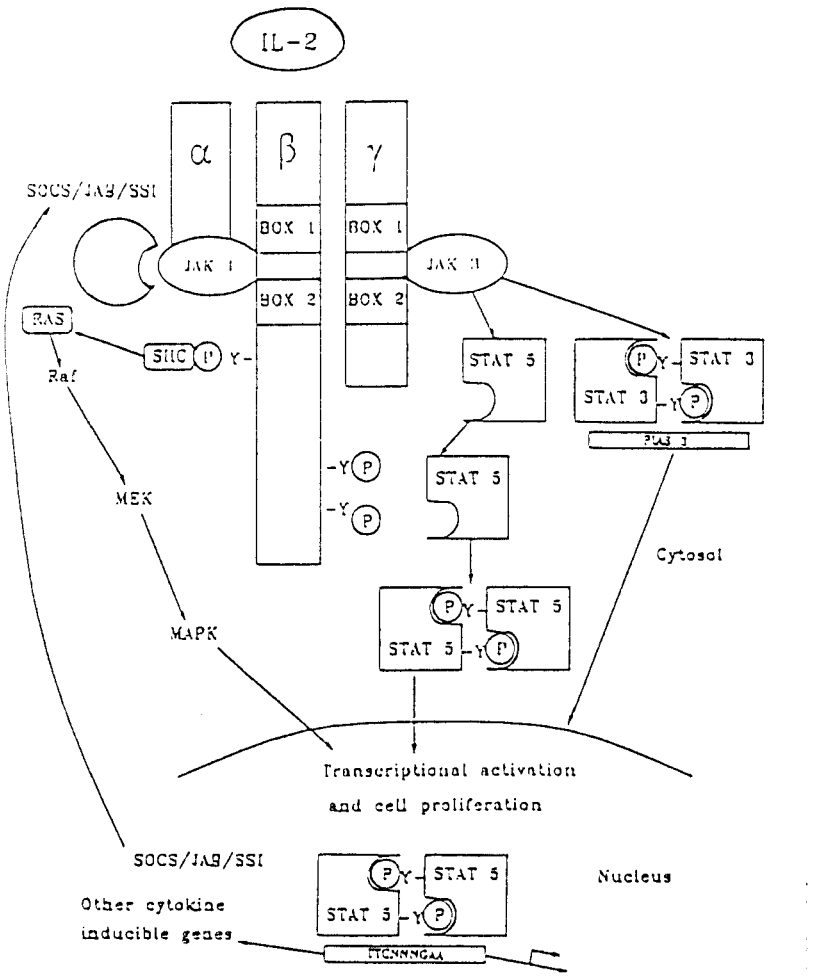



**Fig (3): Schematic of janus protein tyrosine kinase (JAK)-signal transducer and activator of transcription (STAT) paradigm in the context of IL-2 signaling. JAK1 associates with IL-2Rβ while $Jak_3$ associates with IL-2Rγ. This allows the docking of STAT 5 via its $SH_2$ domain, the STATs themselves are tyrosine phosphorylated, dimerize, and translocate to the nucleus, where they modulate expression of target genes. Also stat3 function in the same way. The schematic also indicates that another phosphotyrosine mediates recruitment of adaptor protein (Shc), which then can couple to the proto-oncogen (Ras)/serine-threonine kinase (Raf) / dual-specific tyrosine-serine threonine kinase (MEK) / mitogen-activated protein kinase (MAPK). Also inhibitors of cytokine signalling are shown which are suppressor of cytokine signaling (SOCS), JAK-binding protein (JAB), STAT-induced STAT inhibitor (SSI), and protein inhibitor of activated STAT3 (PIAS3) *(Leonard, 1999; Weiss, 1999; Chen et al., 1998; and Theze et al., 1996).***

# IL-2 RECEPTOR IN DIFFERENT DISEASES:

## X linked severe combined Immunodeficiency Disease (SCID):

SCID is a rare syndrome characterized by profound impairement of both cellular and humoral immunity. Without bone marrow transplanation, affected patients suffer severe and persistent infections, often with opportunistic pathogens, and generally die in infancy. While both x-linked recessive and autosomal form of SCID are recognized, the x-linked form is the most frequent. Patients with X-SCID generally have very low numbers of T cells and natural killer (NK)cells, normal numbers of B cells, but defective B cell responses, IgM can be normal, but immunoglobulins of other classes may be greatly diminished. It is caused by mutations in the IL-2 R gene, the gene encoding the $\gamma$ chain of interleukin-2-receptor (the common $\gamma$ chain for IL-2, 4,7,9,15). This gene is located on the x chromosome.

$JAK_3$ mutations result in an autosomal recessive form of SCID which is indistinguishable from that in XSCID *(Leonard, 1999; Puck, 1996)*.

## Soluble IL-2R $\alpha$ increase in the following diseases:

1- Vitiligo *(Caixia et, al., 1999)*.
2- Graft versus host disease *(Kobayashi et al.,1999$_b$)*.
3- Pulmonary mycobacterial diseases *(Tada et al., 1999)*.
4- Acute bipolar mania *(Tsai et al, 1999)*.
5- Multiple sclerosis *(Rilinska et al., 1999)*.
6- Gastroenteric cancer *(Piancatell et al., 1999)*.
7- Ovarian Cancer *(Wang et al., 1998)*.
8- Gaucher's disease *(Barak et al., 1999)*.
9- Rett syndrome *(Fiumara et al, 1999)*.
10- Atopic dermatitis *(Huang et al., 2000)*.
11- Dialyzer membrane biocompatability *(El-Saeed, 1998)*.
12- Septic neonates *(Sorial, 1997)*.

*Chapter Five:*

# *Immunology of Depression*

# IMMUNOLOGY OF DEPRESSION

It has been hypothesized that the immune system plays a pathogenic role in psychiatric disorders, in particular in major depression. This hypothesis is supported by a number of reports on altered circulating levels and in vitro production of cytokines in this disorder. ***Haack et al., (1999)*** found that circulating levels of interleukin-1 receptor antagonist (IL-1Ra), soluble IL-2 receptor (sIL-2R), tumor necrosis factor-alpha (TNF- alpha), soluble TNF receptors (sTNF-Rp55, STNF-Rp75) and IL-6 were significantly affected by age, the body mass index (BMI), gender, smoking habits, exercise, ongoing or recent infectious diseases, or prior medication. Cytokine or cytokine receptor levels were significantly increased in patients treated with clozapine (sIL-2R, sTNF-Rpz5), lithium (TNF-alpha, sTNF-Rpz5, IL-6) or benzodiazepines (TNF- alpha, sTNF-Rpz5).

Data suggest that the antidepressants currently available including the tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) have the capacity to influence the immune response. In vitro exposure of immune cells to imipramine and desipramine inhibited both mitogen-induced lymphocyte proliferation as well as natural killer cell activity in a dose – dependent fashion. More recent in vitro studies have demonstrated that the TCAs clomipramine and imipramine and the SSRI citalopram are capable of suppressing the secretion of IL-2 by stimulated lymphocytes and IL-1 beta and interferon-gamma by stimulated monocytes ***(Miller, 2000)***.

***Yirmiya (1996); Dantzer et al., (1998)*** deduced that pretreatment of rats with the antidepressant imipramine or fluoxetine has been associated with an attenuation of sickness behavior symptoms following exposure to bacterial endotoxin, a potent inducer of proinflammatory cytokines. In addition several anecdotal reports have indicated that antidepressants successfully

manage symptoms of depression in patients receiving high dose cytokines for immunotherapy ***(Connor and Leonard, 1998)***.

***Anisman et al., (1999$_a$)*** found that dysthymia is associated with elevated IL-1 beta production which was modestly correlated with the severity of symptoms and with the age of illness onset. Sertraline attenuated the symptoms of depression; however, this was not accompanied by normalization of IL-1 beta production which suggested that either the IL-1 beta may be a trait marker of the illness, or that more sustained treatment is necessary to reduce cytokine production.

***Anisman et al, (1999$_b$)*** found IL-2 production was reduced in major depression and dysthmia with typical and atypical features although less so among atypical major depressives. Moreover, IL-2 production in the depressive groups was directly related to plasma norepinephrine (NE) levels. Also ***Weizman et al., (1994)*** demonstrated suppression of IL-1β, IL-2, and IL-3-LA production during the acute phase of depression and their restoration to normal range on recovery.

## Immune correlates of depression:

Depressed subjects are likely to have changes in major immune cell classes with an increase in total white blood cell counts and a relative increase in numbers of neutrophils. However, the relative number of lymphocytes is likely to be reduced in depressed subjects. Depression is reliably associated with a suppression of mitogen-induced lymphocyte proliferation and with a reduction of NK activity. Severity of melancholic symptoms and sleep disturbance appear to moderate the immune changes in depression, but the biological mechanisms that account for the link between these neurovegetative symptoms and depression are not yet known ***(Irwin, 1999)***.

However ***Schleifer et al., (1999)*** found evidence of increased lymphocyte activation to mitogen challenge and decreased natural killer (NK) cell numbers and function during acute depression.

Evidence for immune stimulation in depressive disorder has been obtained. An increased number of $CD4^+$ cells and a higher CD4/CD8 ratio have been observed by ***Muller et al., 1993***. Increased numbers of activated (i.e. $CD25^+$ and $HLA\text{-}DR^+$). Also there is a significant positive correlation between the number of CD25 (IL-2R) on one hand and the CD4/CD8 ratio and number of CD4 cells on the other hand ***(Sluzewaska et al., 1996)***.

Further evidence of activated cellular immunity in major depression is corroborated by the findings of increased transferrin receptors. (CD71) as well as plasma and urinary neopterin concentrations which is a very senstive marker of activation of cell mediated immunity ***(Bonaccorso et al., 1998)***.

While neither ***Landmann et al., (1997)*** nor ***O'Toole et al., (1998)*** found significant difference in plasma neopterin in patients with major depression than normal control, ***Bonaccorso et al., (1998)*** reported that increased urinary excretion of neopterin can be used as a marker for major depression. Also ***Dunbar et al., (1992)*** found elevated serum neopterin concentrations.

Major depression is characterised by decrease in serum dipeptidyl peptidase IV (DPPIV) activity which may be related to the immune activation of cell mediated immunity (CMI) or inflammatory (acute phase response) pathophysiology of major depression ***(Maes et al., 1997)***.

Some studies have shown higher plasma levels of acute phase proteins (APP) such as C- reactive protein, haptoglobin, alpha-1 antitrepsin, alpha-1 acid glycoprotein, or ceruloplasmin, as another sign of immune stimulation in depression ***(Seidel et al, 1995)***. Acute phase proteins are released by hepatocytes in the early phase of inflammation due to monokines e.g. IL-6 and IL-1. Hypozincaemia is another index for an immune activation in depression ***(Maes et al, 1994)***.

In addition decreases in negative acute phase proteins including albumin and transferrin during the acute phase response of inflammation ***(Miller, 2000)***.

Neuroendocrine abnormalities such as dysregulation of hypothalamic pituitary adrenal (HPA) axis in major depression, are associated with an increase in production of monocyte-derived cytokines such as IL-1 and IL-6 in the supernatants of leucocyte cultures *(Maes et al., 1993)*. Furthermore ***Seidel et al., (1995)*** revealed higher concentrations of lymphocytes released cytokines such as interferon-γ and IL-2 and sIL-2R in supernatants of cultured leucocytes suggesting an immune activation in the acute clinical state of the disease. Cytokines are important factors in immune regulation, and proinflammatory cytokines (IL-6, and its soluble receptor, IL-1, IL-1R antagonist, interferon gamma, and sIL-2R) in particular are potent inducers of acute phase response. Moreover proinflammatory cytokines have marked effects on nervous and endocrine system function *(Miller,2000)*.

***McAdams, (1993)*** demonstrated an increase in phagocytosis of monocytes in depressive patients.

***Seidel et al., (1996)*** data support the findings of other authors who have demonstrated an immune activation, and they suggest the existence of an immune inflammatory process in the acute clinical state of depression. In particular, their results suggest a gradual activation and relevance of monocytes dependent upon disease severity and disease outcome. The increase in phagocytic cells, i.e. monocytes and granulocytes, in the acute clinical state of depression suggests the existence of an inflammatory process in this disease. They propose that monocytes in particular, and possibly monocyte- derived cytokines, may play an important role in the acute phase of depression and could provide an explanation for immunological findings in depressive states.

The suppressed in vitro immune response in depressives may be explained by the increased levels of sIL-2R in serum which could induce a state of IL-2 starvation by binding it and limiting the amount of IL-2 necessary for immune cell proliferation and NKC activity. Furthermore lower dipeptidyl

peptidase IV activity may play a role in the diminshed lymphocyte transformation test (LTT) responses in depression *(Maes et al, 1995b)*.

## Stress depression and immunity:

It is by now widely recognized that acute and chronic stress have an impact on the immune system. Acute stress may have a stimulating effect on the immune system, while in the case of chronic stress and in particular in depression- the immune system may be down regulated. However there is considerable individual variability in the immune response to stress. This seems to a large extent to be determined by the subject's way of dealing with stress. The perception and evaluation of a stressor and the specific ways of stress coping may in different ways be related to various aspects of the stress response: Sympathetic nervous system (SNS) activation, and activation of the hypothalamic- pituitary adrenal (HPA) axis, both systems affecting the immune system. Prolonged exposure to stressors or to severe life stresses may outweigh the person's coping resources leading to feelings of depression. The affective changes with the accompanying changes in the HPA axis are one of the hypothesized mechanisms underlying the immune changes in depression *(Olff, 1999)*.

## The relation between central nervous, endocrine and immune systems:

There are two pathways that link the brain and the immune system. These are the autonomic nervous system and the neuroendocrine outflow via the pituitary. Both routes provide biologically active molecules interacting with cells of the immune system *(Ader et al., 1995)*.

### Neural – immune interactions:

Cytokines released by activated immune cells in addition to their role in regulating cellular interactions, are one mean by which the immune system communicates with the CNS and thereby influences behavior. Cytokines mediate informations

between cells of the immune system and the CNS. Interleukins (IL)-1,2,6, interferon gamma (IFNγ) and tumour necrosis factor alpha (TNF-α) are the most relevant activating cytokines known to act on the CNS. Cytokines behave like a network since they can activate cells to produce other cytokines in addition these cytokines influence activation of the HPA axis and are in turn influenced by glucocorticoid secretion *(Ader et al., 1995)*.

Cytokines activate CNS cells in different ways. First several cytokines such as interleukin 1,2, and TNF-α can be transported from the blood into the CNS by active transport mechanisms (Guiterrez et al., 1993). Second, glia cells secrete cytokines after activation by antigenic challenge. Finally, it has been reported that cytokine secretion in the CNS can be stimulated by neurotransmitters. Noradrenaline stimulates the release of IL-6 from astrocytes in vitro in a dose dependent manner, an effect that can be antagonized by blocking the adrenergic receptors. Since IL-6 is closely linked with the function of other cytokines e.g. IL-1,2 and TNF α, this finding indicates that neurotransmitters can activate the cascade of cytokines *(Muller and Ackenheil, 1998)*.

Recent findings show that cytokines are relevant in psychiatric disorders possibly mainly due to their influence on neurotransmitters. The noradrenaline released during stress may act as a cytokine activating stimulus which thus activates immune phenomena mediated by the cytokine cascade. This represents possibly a relevant psychoneuro- immunological regulative mechanism affecting autoimmune disorders, susceptibility to infections and psychiatric disorders *(Muller and Ackenheil, 1998)*.

## Endocrine-immune interactions:

Lymphocytes bear receptors for CRF, adrenocorticotropic hormone (ACTH), and endogenous opioids such as endorphins and encephalins. The endogenous opioids directly influence antigen specific and non specific responses. Although there are

direct immunomodulatory effects of CRF and ACTH, their major effects are exerted through interactions with other hormones and immune system products *(Ader et al., 1995)*.

Glucocorticoids have a strong immunosuppressive effects through a variety of mechanisms, such as induced cell death (aptosis),· inhibition of IL-1,2, and 6 production or secretion and redistribution of peripheral blood mononuclear cells (PBMNC) e.g. depletion of $CD4^+$ T cells *(Maes et al., 1994)*.

IL-2 is produced in blood by activated T lymphocytes and in the CNS, mainly by activated microglia cells. Considering pschiatric disorders, IL-2 effects in the CNS are of particular interest for these reasons: The highest concentration of interleukin-2 receptor (IL-2R) is found in the hippocampus, psychotic phenomena occurs after application of IL-2 and it has an immense effect on the dopaminergic neurotransmitters. IL-2 has been shown to stimulate ACTH secretion by anterior pituitary cells and has been implicated in pathophysiological processes of the anterior pituitary and brain in several major psychiatric disorders· *(Muller and Ackenheil, 1998)*. However, ***Petitto et al, (1997)*** confirmed that the IL-2Rβ is constitutively expressed by pituitary cells and is involved in mediating intracellular signal transduction processes induced by IL-2 in this endocrine cell line.

# *Subjects and Methods*

# SUBJECTS AND METHODS

## Subjects:

### (I) Patients group :

This group consisted of 60 Egyptian patients who were experiencing an episode of depression recruited in a cross sectional case control study.

**A) Inclusion Criteria:**

* Age ranging from seven to eighteen years because most children cannot use language to effectively communicate information until age 7 ***(Poznanski, 1982)***.
* All cases diagnosed as having an episode of depression.
* Sex : Both males (n=22) (36.7%) and females (n=38) (63.3%).
* Can read and write (self rated).

**B) Exclusion criteria:**

* Substance use disorders (SUD).
* Patients who had taken any medication which might impair cell mediated immunity (e.g. oral corticosteroids), Benzodiazepine, Lithium, Clozapine, Tricyclic Antidepressants (TCAs), Selective Serotonine Reuptake Inhibitor (SSRIs), or Anticancer drugs as Methotrexate, Bleomycin ...etc.), 2 weeks before the study.
* Patients with any relevant physical illness (e.g. malignancy, autoimmune disease, bacterial or viral illness within the last month).

**C) Selection of cases and Site of the Study:**

The cases were selected from the institute of psychiatry, Faculty of medicine, Ain shams university for 1.5 years from October 1998 to April 2000.

## (II) Control Group:

The control group consists of 20 Egyptian children with no physical disease or depressive disorder. They were matched for age, sex and socio economic status as far as possible with the patient group. They were chosen from healthy relatives of the patients.

# METHODS :

## Cases and controls are subjected to:

1) **Psychiatric Interview:** psychiatric interviewing of parents of suspected cases to confirm the diagnosis based on *ICD-10 (1992)* and to elicit some risk factors which predispose to this disorder.

2) **Complete physical examination:** to exclude any concomitant physical illness.

3) **The Arabic version of children Depression Inventory (CDI) (Appendix).** It was prepared by ***Abdel Fattah in (1988)***. Its items depends on children depression inventory of ***Kovacs (1983)***. It is a depression screening questionnaire developed specifically for children and adolescents and is actually being evaluated for its ability to detect asymptomatic depressive symptoms and disease ***(Kamerow, 2000)***. CDI was applied by the researcher on cases and controls in order to assure that controls are not with significant depressive symptomatology and to assure the diagnosis of patients.

CDI is 27 items-self report-questionnaire that includes cognitive, affective and behavioral aspects of depression in children. The child is asked to endorse the one of the three descriptions that best describes the way he or she has been feeling and thinking during the preceding 2 weeks. Responses are scored on a 0-2 scale. With Zero representing the absence of a particular depressive symptoms and one is representing the moderate form of this symptoms, while two representing the severe form of the

symptom. Thus the CDI total score ranged from 0-54. A cut off score of 13 on the CDI could identify the upper 10% of the children as depressed while a cut off score of 19 representing the 90$^{th}$ percentile, has been recommended in several investigation, i.e. a cut off score of 16 represents 50$^{th}$ percentile (and this is the cut off score used here by the researcher) ***(Kovacs 1981; Smucker et al., 1989; Ollendick and Yule; 1990; and Larsson and Melin, 1992)***. It is to be noticed that the researcher intentionally chosen control below score 12 in order to make difference between patients and controls.

**4) Assessment of the Socio-economic status of the family:**

The scoring system which was used by the researcher in the study for assessment of the socioeconomic status (S.E.S) is the modified socioeconomic scale for Egyptian families described by ***(El-Shakhs, 1995) (Appendix)*** in which the researcher used the following parameters in her evaluation:

**First** : Occupation of father and mother (9 levels).

**Second** : Level of education of father and mother (8 levels).

**Third** : Income per capita per month (7 levels).

The level of the socioeconomic status is calculated by the following equation:

$X = A + B_1 S_1 + B_2 S_2 + B_3 S_3 + B_4 S_4$

Where X = the socioeconomic level to be calculated.

A = fixed number = 2.259.

B = Variables calculated using Dummy variable method where:

$B_1 = 1.016$ $B_2 = 0.886$

$B_3 = 0.622$ $B_4 = 0.013$

While ($S_1$) score of income per capita per month

($S_2$) score of work of father.

($S_3$) score of education of father.

($S_4$) score of work of mother.

So the equation becomes:

$X = 2.259 + 1.016\ (S_1) + 0.886\ (S_2) + 0.622\ (S_3) + 0.013\ (S_4)$

Finally, the data were coded, scored and used to classify the families into 7 levels (1-7) (Appendix)

**5) Serum was used for detection of soluble IL-2R using the enzyme linked immunosorbent assay (ELISA)** ***(Diaclone Research, 2000).***

**Principle of the method:**

A polyclonal antibody specific for sIL-2R has been coated onto the wells of the microtiter strips provided which can bind any sIL-2R present in the serum of this sample.

**Reagents and tools provided:**

1. 96-wells microtiter plates.
2. Plastic cover.
3. Control : 470+/-94 Pg/ml.
4. Standard buffer diluent.
5. Biotinylated anti-sIL-2R.
6. Biotinylated antibody diluent.
7. Streptavidin- HRP.
8. HRP- Diluent
9. Washing buffer.
10. Chromogen TMB
11. H2So4 : stop reagent

**Sample collection :**

5ml of blood were collected without anticoagulant. Serum were separated and stored frozen at-70°C until used to estimate sIL-2R.

## Assay procedure :

(1) Add 100 µl of sample or diluted standard or control.

(2) Add 50µl of diluted biotinylated anti-IL-2R to all wells.

(3) Incubate for 3 hours at room temperature.

(4) Add 100 µl of HRP- Streptavidin conjugate.

(5) Incubate the micro well strips at room temperature for 30min.

(6) Add 100µl of ready to- use TMB substrate solution into all wells and incubate in the dark for 12-15 minutes at room temperature.

(7) Incubation time of the substrate solution is usually determined by the ELISA reader performances (maximum 20 minutes).

(8) Add 100 µl $H_2So_4$ to stop the enzyme substrate reaction.

(9) Read absorbance of each well at 450nm as the primary wavelength.

**Data analysis:**

Generate a linear standard curve by plotting the average absorbance on the vertical axis versus the corresponding s IL-2R standard concentration on the horizontal axis. The amount of sIL-2R in each sample is determined by extraploting optical density (OD) values to sIL-2R concentrations using the standard curve.

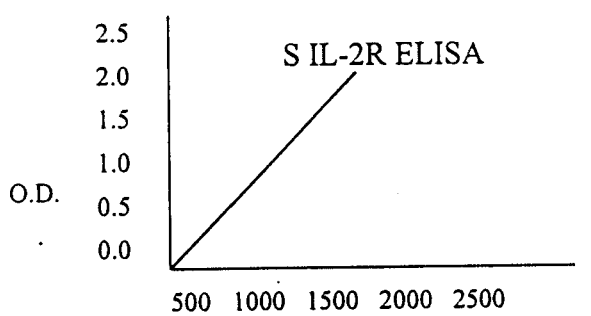



**Fig (4): Typical sIL-2R standard curve ranging from 68.75 to 2200 Pg/ml.**

## Statistical Methods :

The clinical and laboratory data were recorded on an "investigative report form". These data were analyzed using statistical analysis computer program, version 2.0 – by Microsoft to obtain:

## Descriptive statistics:

1) Mean (x):

$$x = \frac{\Sigma x}{n}$$

$$\Sigma x = x_1 + x_2 + \ldots\ldots + x_n$$

*Where:*

X = The mean.

n = Number of data items.

$\Sigma x$ = The summation of all observations.

2) The standard deviation (S.D.):

$$S.D. = \frac{\Sigma x^2 - n\bar{x}^2}{n-1}$$

*Where :*

SD = Standard deviation of the sample.

$\Sigma x^2$ = The summation of the squares of observations. The population is assumed to be n-1.

3. Minimum and maximum values (range).

## Analytic Statistics:

1. Comparisons between two groups were done by the students T-test while comparisons between more than two group means, were performed using the analysis of variance

procedures (ANOVA), which is an extension to the student's T-test used when comparing more than two groups.

P value = level of significance

P > 0.05→ Insignificant.

P< 0.05 → Significant.

$$t = \frac{\textit{Difference} \text{ between 2means}}{\sqrt{SE_1^{\,2} + SE_2^{\,2}}}$$

Qualitative variables expressed as percentages are compared in different groups using the chi-square Test ($x^2$).

2x2 Chi-square (2x2 Contingency Table)

| | **Positive** | **Negative** | |
|---|---|---|---|
| **Attribute Absent** | a | b | a+b |
| **Attribute Present** | c | d | a+d |
| | a+c | b+d | n |

n= a+b+c+d

$$\mathbf{X2} = \frac{N\,(|ad-bc| - \tfrac{1}{2}\,n)^2}{(a+b)\,(c+d)\,(a+c)\,(b+d)}$$

**Significance of results:**

Non significant (NS) if P>0.05

Significant (S) if P<0.05

High significant (HS) if P<0.01

2. Variables were correlated in all possible combinations against each other. The correlation coefficient (r) is a measure of the degree of closeness of the linear relationship between two variables (x and y) σ always lies between –1 and +1.

$$r = \frac{\Sigma xy - \dfrac{\Sigma x \Sigma y}{n}}{\sqrt{\Sigma x^2 - \dfrac{(\Sigma x)^2}{n}} \cdot \sqrt{\Sigma y - \dfrac{(\Sigma y)^2}{n}}}$$

Where:

x= the value of the first variable

y= the value of the 2nd variable.

n= the number of variables

Positive values of "r" indicate a tendency of x and y to increase together. Negative values of "r" indicate a tendency of x to increase with decrease in y.

***N.B:*** Fisher's exact probability is used if any of expected frequencies are less than or equal to 5.

# *Results*

# RESULTS

In this study 60 cases were divided into mild moderate and severe subgroups of depression each matching control (no = 20).

The results of this study were represented in table (6) to (24) and Fig (5) to (19).

**Table (6): Age in years in cases and controls.**

| | Entire Cases (no=60) | Control (no=20) |
|---|---|---|
| **Range** | 7-18 | 8-18 |
| **Mean** | 14.53 | 14.6 |
| **Standard deviation (SD)** | 3.33 | 3.57 |
| **t** | 0.88 | |
| **P** | > 0.05 (Insignificant) | |

This table demonstrates that the cases and their control group were chosen of nearly the same age.

**Table (7): Sex distribution in the cases and controls.**

| | Entire Cases no (%) | Control no(%) |
|---|---|---|
| **Male** | 22 (36.7%) | 8 (40%) |
| **Female** | 38 (63.3%) | 12 (60%) |
| **$X^2$** | 1.2 | |
| **P** | > 0.05 (Insignificant) | |

This table shows that sex in both cases and control were matched.

*N.B:* On comparing male group (n=22) (36.7%) and female group (n=38) (63.3%) in the entire case group a highly significant difference was obtained ($x^2 = 8.53$, $P<0.01$).

**Table (8): Socio Economic Standard (SES) of the cases and controls.**

| | Entire Cases no = 60 | Control no = 20 |
|---|---|---|
| Mean | 4.67 | 4.95 |
| S.D. | 1.79 | 2.1 |
| t | 1.56 | |
| P | > 0.05 (Insignificant) | |

As regards socioeconomic status there was no significant difference between the entire cases and control.

*N.B:* Scores of S.E.S are: 1=Very low, 2=Low, 3=Below average, 4= Average, 5=Above average, 6= High, 7= Very high.

**Table (9): Age in different subgroups of patients.**

| | Mild no=20 | Moderate no=20 | Severe no=20 |
|---|---|---|---|
| Range | 7-18 | 10-18 | 9-18 |
| Mean | 14.4 | 14.8 | 14.4 |
| S.D. | 3.5 | 2.8 | 3.8 |
| ANOVA Test P | P > 0.05 (Insig.) | P > 0.05 (Insig.) | |
| | P > 0.05 (Insig.) | | |

Insig. = Insignificant

There is no significant difference between subgroups of patients as regard age.

**Table (10): Sex in different subgroups of patients**

| | Mild | | Moderate | | Severe | |
|---|---|---|---|---|---|---|
| | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** |
| | no (%) | no (%) | no (%) | no (%) | no (%) | no (%) |
| | 10 (50%) | 10 (50%) | 4 (20%) | 16(80%) | 8 (40%) | 12 (60%) |
| $X^2$ | 2.6 | | | | | |
| P | >0.05 (Insig.) | | | | | |

Insig. = Insignificant.

It is shown that there is increase in number of female gender in both moderate 16 (80%), and severe group 12 (60%).

**Table (11): Depression symptoms according to Children Depression Inventory (CDI) in all groups of patients and controls.**

| Depressive Symptoms | Mild no (%) | Moderate no (%) | Severe no (%) | Control no (%) |
|---|---|---|---|---|
| 1. Sadness | | | | |
| 0 Absent | 0 (0%) | 0 (0%) | 0 (0%) | 19 (95%) |
| 1 Moderate | 20 (100%) | 14 (70%) | 14 (70%) | 1 (5%) |
| 2 Severe | 0 (%) | 6 (30%) | 6 (30%) | 0 (0%) |
| P | <0.01 (H.Sig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 2. Pessimism | | | | |
| 0 Absent | 10 (50%) | 4 (20%) | 0 (0%) | 9 (45%) |
| 1 Moderate | 10 (50%) | 12(60%) | 12 (60%) | 11 (55%) |
| 2 Severe | 0 (0%) | 4 (20%) | 8 (40%) | 0 (0%) |
| P | <0.05 (Sig) | <0.05 (Sig) | <0.01 (H.Sig) | |
| 3. Sense of failure | | | | |
| 0 Absent | 14 (70%) | 10 (50%) | 0 (0%) | 19 (95%) |
| 1 Moderate | 6 (30%) | 8 (40%) | 10 (50%) | 1 (5%) |
| 2 Severe | 0 (0%) | 2 (10%) | 10 (50%) | 0 (0%) |
| P | <0.05 (Sig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 4. Loss of interest | | | | |
| 0 Absent | 0 (%) | 0 (0%) | 0 (0%) | 10 (50%) |
| 1 Moderate | 18 (90%) | 18 (90) | 8 (40%) | 10 (50%) |
| 3 Severe | 2 (10%) | 2 (10%) | 12 (60%) | 0 (0%) |
| P | <0.01 (H.Sig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |

**Table (11) (cont.): Depression symptoms according to Children Depression Inventory (CDI) in all groups of patients and controls.**

| Depressive Symptoms | Mild no (%) | Moderate no (%) | Severe no (%) | Control no (%) |
|---|---|---|---|---|
| 5. Faulty behavior | | | | |
| 0 Absent | 14 (70%) | 10 (50%) | 6 (30%) | 20 (100%) |
| 1 Moderate | 2 (10%) | 10 (50%) | 4 (20%) | 0 (0%) |
| 2 Severe | 4 (20%) | 0 (0%) | 10 (50%) | 0 (0%) |
| P | <0.05 (Sig) | >0.01 (H.Sig) | <0.01 (H.Sig) | |
| 6.Anticipated anxiety | | | | |
| 0 Absent | 8 (40%) | 4 (20%) | 6 (30%) | 8 (40%) |
| 1 Moderate | 12 (60%) | 16 (80%) | 10 (50%) | 11 (55%) |
| 2 Severe | 0 (0%) | 0 (0%) | 4 (20%) | 1 (5%) |
| P | >0.05 (Insig) | >0.05 (Insig) | >0.05 (Insig) | |
| 7. Self hated | | | | |
| 0 Absent | 16 (80%) | 6 (30 %) | 6 (30%) | 17 (85%) |
| 1 Moderate | 0 (0%) | 12 (60%) | 10 (50%) | 2 (10%) |
| 2 Severe | 4 (20 %) | 2 (10%) | 4 (20%) | 1 (5%) |
| P | >0.05 (Insig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 8. Self reproach | | | | |
| 0 Absent | 16 (80%) | 12 (60%) | 2 (10%) | 18 (90%) |
| 1 Moderate | 2 (10%) | 6 (30%) | 12 (60%) | 1 (5%) |
| 2 Severe | 2 (10%) | 2 (10%) | 6 (30%) | 1 (5%) |
| P | >0.05 (Insig) | >0.05 (Insig) | <0.01 (H.Sig) | |
| 9. Suicidal ideation | | | | |
| 0 Absent | 14 (70%) | 0 (0%) | 2 (10%) | 13 (65%) |
| 1 Moderate | 4 (20%) | 20(100%) | 18 (90%) | 7 (35%) |
| 2 Severe | 2 (10%) | 0 (0%) | 0 (0%) | 0 (0%) |
| P | >0.05 (Insig) | <0.001(H.Sig) | <0.001 (H.Sig) | |
| 10. Tearful | | | | |
| 0 Absent | 14 (70%) | 8 (40%) | 4 (20%) | 17 (85%) |
| 1 Moderate | 4 (20%) | 4 (20%) | 4 (20%) | 2 (10%) |
| 2 Severe | 2 (10%) | 8 (40%) | 12 (60%) | 1 (5%) |
| P | <0.05 (Sig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 11. Decreased tolerance to frustration | | | | |
| 0 Absent | 12 (60%) | 8 (40%) | 6 (30%) | 15 (75%) |
| 1 Moderate | 6 (30%) | 10 (50%) | 10 (50%) | 4 (20%) |
| 2 Severe | 2 (10%) | 2 (10%) | 4 (20%) | 1 (5%) |
| P | >0.05 (Insig) | >0.05 (Insig) | <0.01 (Insig) | |
| 12. Decreased Social interest | | | | |
| 0 Absent | 10 (50%) | 8 (40%) | 6 (30%) | 19 (95%) |
| 1 Moderate | 4 (20%) | 12 (60%) | 6 (30%) | 1 (5%) |
| 2 Severe | 6 (30%) | 0 (0%) | 8 (40%) | 0 (0%) |
| P | <0.01 (H.Sig) | <0.001(H.Sig) | <0.01 (H.Sig) | |
| 13. Hesitation | | | | |
| 0 Absent | 4 (20%) | 4 (20%) | 4 (20%) | 10 (55%) |
| 1 Moderate | 8 (40%) | 12 (60%) | 10 (50%) | 8 (30%) |
| 2 Severe | 8 (40%) | 4 (20%) | 6 (30%) | 2 (15%) |
| P | >0.05 (Insig) | >0.05 (Insig) | <0.01 (H.Sig) | |

**Table (11) (cont.): Depression symptoms according to Children Depression Inventory (CDI) in all groups of patients and controls.**

| Depressive Symptoms | Mild no (%) | Moderate no (%) | Severe no (%) | Control no (%) |
|---|---|---|---|---|
| 14. Negative body image | | | | |
| 0 Absent | 14 (70%) | 4 (20%) | 4 (20%) | 13 (65%) |
| 1 Moderate | 4 (20%) | 14 (70%) | 6 (30%) | 7 (35%) |
| 2 Severe | 2 (10%) | 2 (10%) | 10 (50%) | 0 (0%) |
| P | >0.05 (Insig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 15. Decreased motivation to school | | | | |
| 0 Absent | 6 (30%) | 6 (30%) | 4 (20%) | 10 (50%) |
| 1 Moderate | 8 (40%) | 10 (50%) | 10 (50%) | 8 (40%) |
| 2 Severe | 6 (30%) | 4 (20%) | 6 (30%) | 2 (10%) |
| P | >0.05 (Insig) | >0.05 (Insig) | >0.05 (Insig) | |
| 16. Disturbed sleep | | | | |
| 0 Absent | 4 (20%) | 2 (10%) | 4 (20%) | 11 (55%) |
| 1 Moderate | 12 (60%) | 14 (70%) | 10 (50%) | 9 (45%) |
| 2 Severe | 4 (20%) | 4 (20%) | 6 (30%) | 0 (0%) |
| P | >0.05 (Insig) | <0.01 (H.Sig) | >0.01 (H.Sig) | |
| 17. Exhaustion | | | | |
| 0 Absent | 0 (0%) | 0 (0%) | 0 (0%) | 18 (90%) |
| 1 Moderate | 18 (90%) | 12 (60%) | 6 (30%) | 1 (5%) |
| 2 Severe | 2 (10%) | 8 (40%) | 14 (70%) | 1 (5%) |
| P | <0.01(H.Sig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 18. Reduced appetite | | | | |
| 0 Absent | 6 (30%) | 6 (30%) | 0 (0%) | 14 (70%) |
| 1 Moderate | 6 (30%) | 6 (30%) | 8 (40%) | 1 (5%) |
| 2 Severe | 8 (40%) | 8 (40%) | 12 (60%) | 5 (15%) |
| P | <0.01(H.Sig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 19. Somatic preoccupation | | | | |
| 0 Absent | 10 (50%) | 4 (20%) | 4 (20%) | 18 (90%) |
| 1 Moderate | 6 (30%) | 8 (40%) | 8 (40%) | 1 (5%) |
| 2 Severe | 4 (20%) | 8 (40%) | 8 (40%) | 1 (5%) |
| P | <0.05 (Sig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 20. Loneliness | | | | |
| 0 Absent | 12 (60%) | 0 (0%) | 4 (20%) | 15 (75%) |
| 1 Moderate | 4 (20%) | 12 (60%) | 10 (50%) | 5 (25%) |
| 2 Severe | 4 (20%) | 8 (40%) | 6 (30%) | 0 (0%) |
| P | >0.05 (Insig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 21. Disinterest in school | | | | |
| 0 Absent | 12 (60%) | 6 (30%) | 4 (20%) | 14 (70%) |
| 1 Moderate | 6 (30%) | 12 (60%) | 10 (50%) | 6 (30%) |
| 2 Severe | 2 (10%) | 2 (10%) | 6 (30%) | 0 (0%) |
| P | >0.05 (Insig) | <0.05 (Sig) | <0.01 (H.Sig) | |
| 22. Social isolation | | | | |
| 0 Absent | 10 (50%) | 2 (10%) | 4 (20%) | 10 (50%) |
| 1 Moderate | 8 (40%) | 12 (60%) | 12 (60%) | 9 (45%) |
| 2 Severe | 2 (10%) | 6 (30%) | 4 (20%) | 1 (5%) |
| P | >0.05 (Insig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |

**Table (11) (cont.): Depression symptoms according to Children Depression Inventory (CDI) in all groups of patients and controls.**

| Depressive Symptoms | Mild no (%) | Moderate no (%) | Severe no (%) | Control no (%) |
|---|---|---|---|---|
| 23. Decreased scholastic achievement | | | | |
| 0 Absent | 8 (40%) | 6 (30%) | 4 (20%) | 11 (55%) |
| 1 Moderate | 12 (60%) | 10 (50%) | 10 (50%) | 9 (45%) |
| 2 Severe | 0 (0%) | 4 (20%) | 6 (30%) | 0 (0%) |
| P | >0.05 (Insig) | >0.05 (Insig) | <0.01 (H.Sig) | |
| 24. Self criticism | | | | |
| 0 Absent | 10 (50%) | 14 (70%) | 2 (10%) | 12 (60%) |
| 1 Moderate | 8 (40%) | 4 (20%) | 8 (40%) | 8 (40%) |
| 2 Severe | 2 (10%) | 2 (10%) | 10 (50%) | 0 (0%) |
| P | >0.05 (Insig) | >0.05 (Insig) | <0.01 (H.Sig) | |
| 25. Sense of unwelcome | | | | |
| 0 Absent | 18 (50%) | 4 (20%) | 4 (20%) | 20 (100%) |
| 1 Moderate | 2 (10%) | 10 (50%) | 10 (50%) | 0 (0%) |
| 2 Severe | 0 (0%) | 6 (30%) | 6 (30%) | 0 (0%) |
| P | >0.05 (Insig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 26. Disobedience | | | | |
| 0 Absent | 14 (70%) | 6 (30%) | 4 (20%) | 14 (70%) |
| 1 Moderate | 6 (30%) | 10 (50%) | 10 (50%) | 6 (30%) |
| 2 Severe | 0 (0%) | 4 (20%) | 6 (30%) | 0 (0%) |
| P | No difference | <0.01 (H.Sig) | <0.01 (H.Sig) | |
| 27. Social troubles | | | | |
| 0 Absent | 12 (60%) | 6 (30%) | 6 (30%) | 15 (75%) |
| 1 Moderate | 8 (40%) | 10 (50%) | 6 (30%) | 4 (20%) |
| 2 Severe | 0 (0%) | 4 (20%) | 8 (40%) | 1 (5%) |
| P | >0.05 (Insig) | <0.01 (H.Sig) | <0.01 (H.Sig) | |

Sig = Significant.
Insig = Insignificant
H.Sig = Highly Significant
Prob = Probability

*N.B:* Chi square was used in this table to calculate the significance between each subgroup of depression and control group except when the number of cases and controls were zero percent (in items no 3 and 25 in mild group); fishers exact probability was used then.

Table (11) demonstrates that: Sadness, loss of interest and exhaustion were found in all depressed cases of this study (100%).

Other important symptoms in severe group of depression:

- With (100%) included: Pessimism, sense of failure, and reduced appetite.
- With (90%) included: Suicidal ideation, and self reproach.
- With (80%) included: Somatic preoccupation, loneliness, and social isolation.

While in moderate group of depression other important symptoms:

- With.(100%) included: Suicidal ideation, and loneliness.
- With (90%) included: Social isolation.
- With (80%) included: Somatic symptoms and pessimism.

Disinterest in school were 80% in severe group and decreased scholastic achievement while decreased motivation to school was 80% in both moderate and severe group. N.B: All these symptoms that affect school performance have high significant difference between the severe group and the control group where $P<0.01$. However only decreased motivation to school has insignificant difference between either moderate or severe and control group (where $P>0.05$).

On comparing suicidal ideation in moderate and severe groups by fisher exact probability an insignificant difference was obtained ($P>0.05$).

**Table (12): Comparison between cases and controls as regard stressors**

| Stressors | Cases no (%) | Control no (%) | $X^2$ / P |
|---|---|---|---|
| - Living with two parents | 22 (36.7%) | 15 (75%) | $X^2 = 10.02$ |
| - Living with one parent | 36 (60%) | 5 (25%) | P < 0.01 H.S. |
| - Living with no parent | 2 (3.3%) | 0 (0%) | |
| - Maternal psychopathology | 18 (30%) | 1(5%) | $X^2 = 34.8$ |
| - No maternal psychopathology | 42 (70%) | 19 (95%) | P < 0.01 H.S. |

H.S = Highly Significant

This table shows a high significant difference between cases with depression and control group as regard stressors (P<0.01). These stressors are loss of one or both parents (i.e. living with one or no parent), or maternal psychopathology.

**Table (13): Comparison between all patients and controls as regard sIL-2R.**

| sIL-2R (pg/ml) | Entire Cases no=60 | Control no =20 |
|---|---|---|
| Range | 1185-2200 | 1095-1845 |
| Mean | 1719.8 | 1536 |
| S.D. | 253.8 | 308.3 |
| t | 2.65 | |
| P | <0.05 Significant | |

As shown there is a significant difference between sIL-2R in the entire cases and control (P<0.05).

**Table (14): Comparison between each subgroup of patients and controls as regard sIL-2R.**

| SIL-2R (pg/ml) | Mild no=20 | Moderate no=20 | Severe no=20 | Control no=20 |
|---|---|---|---|---|
| Range | 1185-1995 | 1380-2200 | 1740-2180 | 1095-1845 |
| X | 1586 | 1926 | 2015 | 1536 |
| S.D. | 224.3 | 255.7 | 156.4 | 253.8 |
| t and P value | ●----------● t=0.66 (P>0.1) Insignificant. | | | |
| | | ●----------● t= 4.84 (P< 0.005) Highly Significant | | |
| | | | ●----------● t=7.19 (P<0.005) Highly Significant | |
| ANOVA | On comparing all groups of patients a significant difference between mild and moderate and between mild and severe subgroups of depression was found (P<0.05) | | | |

This table demonstrates that there is a high significant difference between moderate group of depression and control group also between severe group of depression and control group as regards sIL-2R (using t test) where $P < 0.005$ (Highly Significant). Also using ANOVA test there is a high significant difference between mild and moderate group of depression and also between mild and severe group of depression. On the contrary when comparing moderate and severe groups of depression by ANOVA test, there was insignificant difference between both. Again on comparing mild group of depression and control an insignificant difference was detected i.e. sIL-2R was related to clinical severity of depressive illness.

**Table (15): Difference between cases & controls as regard sIL-2R in different age groups.**

| age / sIL-2R | Entire Cases no=60 | | Control group no=20 | |
|---|---|---|---|---|
| Age | 7-12 years (no =14) (23%) | 13-18 years (no =46) (56%) | 7-12 years (no =4) (20%) | 13-18 years (no =16) (80%) |
| Range | 1400-2130 | 1185-2200 | 1860-2180 | 1740-2180 |
| Mean±SD | 1900±260 | 1790.4±378 | 1660±316 | 1494.7±277 |
| t | 1.01 | | 1.28 | |
| P | > 0.05 Insignificant | | > 0.05 Insignificant | |

This table demonstrates that the level of sIL-2R in the different age groups either in cases or controls shows an insignificant difference.

**Table (16): Comparison between male and female cases as regard sIL-2R.**

| sex / sIL-2R | Male no=22 | Female no=38 |
|---|---|---|
| Range | 1400-2190 | 1185-2200 |
| Mean | 1851.3 | 1795.6 |
| S.D. | 295.4 | 387.9 |
| t | 0.5 | |
| P | > 0.05 Insignificant | |

This table shows that the level of sIL-2R in males and females in the entire patients group has insignificant difference.

**Table (17): Difference between sIL-2R in both male and female in all subgroups of patient and control**

| Groups | Male Mean±SD | Female Mean±SD | t | P |
|---|---|---|---|---|
| Mild | 1558±126 | 1614±298 | 0.55 | P>0.05 |
| Moderate | 2050±165.5 | 1796.6±507 | 0.97 | P>0.05 |
| Severe | 2118.75±49.6 | 1945.8±166.3 | 2.84 | P<0.01 |
| Control | 1581.3±310.6 | 1468.13±120 | 0.98 | P>0.05 |

P>0.05 = Insignificant P<0.01= Highly significant

This table demonstrates that IL-2R is positively related to male sex and to increased severity of depression. (P<0.01) (H.Sig).

**Table (18): Difference between all cases with no maternal psychopathology versus cases with maternal psychopathol-ogy as regard sIL-2R.**

| M.Psy / sIL-2R (pg/ml) | No Maternal psychopathology No=42 | Maternal psychopathology No=18 |
|---|---|---|
| Range | 1185-2190 | 1740-2200 |
| Mean±S.D. | 1781±296 | 1896.9±464.9 |
| t | 1.16 | |
| P | P> 0.05 Insignificant | |

M.Psy = Maternal psychopathology

This table demonstrates that sIL-2R in all cases with no maternal psychopathology versus cases with maternal psychopathology shows an insignificant difference.

**Table (19): Difference between each subgroup of patient with maternal psychopathology versus no maternal psychopathology as regard sIL-2R.**

| M.Psy / IL-2 | Moderate | | Severe | |
|---|---|---|---|---|
| | No M. Psy. (no=12) | M. Psy. (no=8) | No M. Psy. (no=10) | M. Psy. (no=10) |
| Mean | 1846.67 | 1848 | 2094 | 1936 |
| S.D. | 271.5 | 691 | 68 | 182 |
| t | 0.01 | | 2.57 | |
| P | >0.05 Insignificant | | <0.05 Significant | |

M.Psy = Maternal psychopathology

This table demonstrates that maternal psychopathology have significant difference on the levels of sIL-2R only in the severe depressive group.

*N.B.*: No relation could be elicited in the mild group because maternal psychopathology in whole group was zero.

**Table (20): Difference between cases living with no or one parent versus cases living with two parents as regards sIL-2R.**

| sIL-2R (pg/ml) / no of parents | Living with no or one parent (no=32) | Living with two parents (no=22) |
|---|---|---|
| Range | 1185-2190 | 1530-2200 |
| Mean±S.D. | 1807.5±412.99 | 1830.9±231.5 |
| t | 0.24 | |
| P | > 0.05 Insignificant | |

This table demonstrates that sIL-2R level in cases living with no or one parent versus two parents shows an insignificant difference.

**Table (21): Difference between cases with score 1 or 2 in CDI (Suicide positive) versus cases with score zero in CDI (suicide negative) as regard sIL-2R.**

| no of parents / sIL-2R (pg/ml) | Suicide negative (Score Zero) no=16 | Suicide positive (Score one and two) no=44 |
|---|---|---|
| Range<br>Mean±S.D. | 1400-2100<br>1708.75±238 | 1185-2190<br>1855.114±384 |
| t | 1.42 | |
| P | > 0.05 Insignificant | |

CDI = Children Depression Inventory.

This table shows that sIL-2R in cases with score 1 or 2 (CDI) versus cases with score zero have no significant difference.

**Table (22): Difference between cases with score zero versus score 1 or 2 in CDI sleep disorder as regards sIL-2R.**

| Sleep disorder / SIL-2R (pg/ml) | No sleep disorder (Score zero according to CDI) no=10 | Sleep disorder (Score 1 or 2 according to CDI) no=50 |
|---|---|---|
| Range<br>Mean±S.D. | 1680-2180<br>1921±199.7 | 1185-2200<br>1772.6±402 |
| t | 1.12 | |
| P | P> 0.05 Insignificant | |

CDI = Children Depression Inventory

This table demonstrates that sIL-2R is cases with zero score versus score 1 or 2 in CDI sleep disorder shows an insignificant difference.

**Table (23): Difference between cases with zero or 1 or 2 score in C.D.I in sleep disorder as regard sIL-2R.**

| Sleep disorder / sIL-2R (pg/ml) | Scores of sleep disorders according to CD.I | | |
|---|---|---|---|
| | O= absent No=10 | 1=moderate no=36 | 2= severe no=14 |
| Mean<br>S.D. | 1732.5<br>337.3 | 1595<br>372.43 | 1412<br>307.54 |
| ANOVA | On comparing all groups of sleep disorder (0, 1 & 2) a significant difference between score 0 and score 2 groups was obtained (P<0.05) | | |

This table demonstrates that sIL-2R level in cases with score zero sleep disorder versus score two shows significant difference.

**Table (24): Correlation between sIL-2R and different items in the entire cases.**

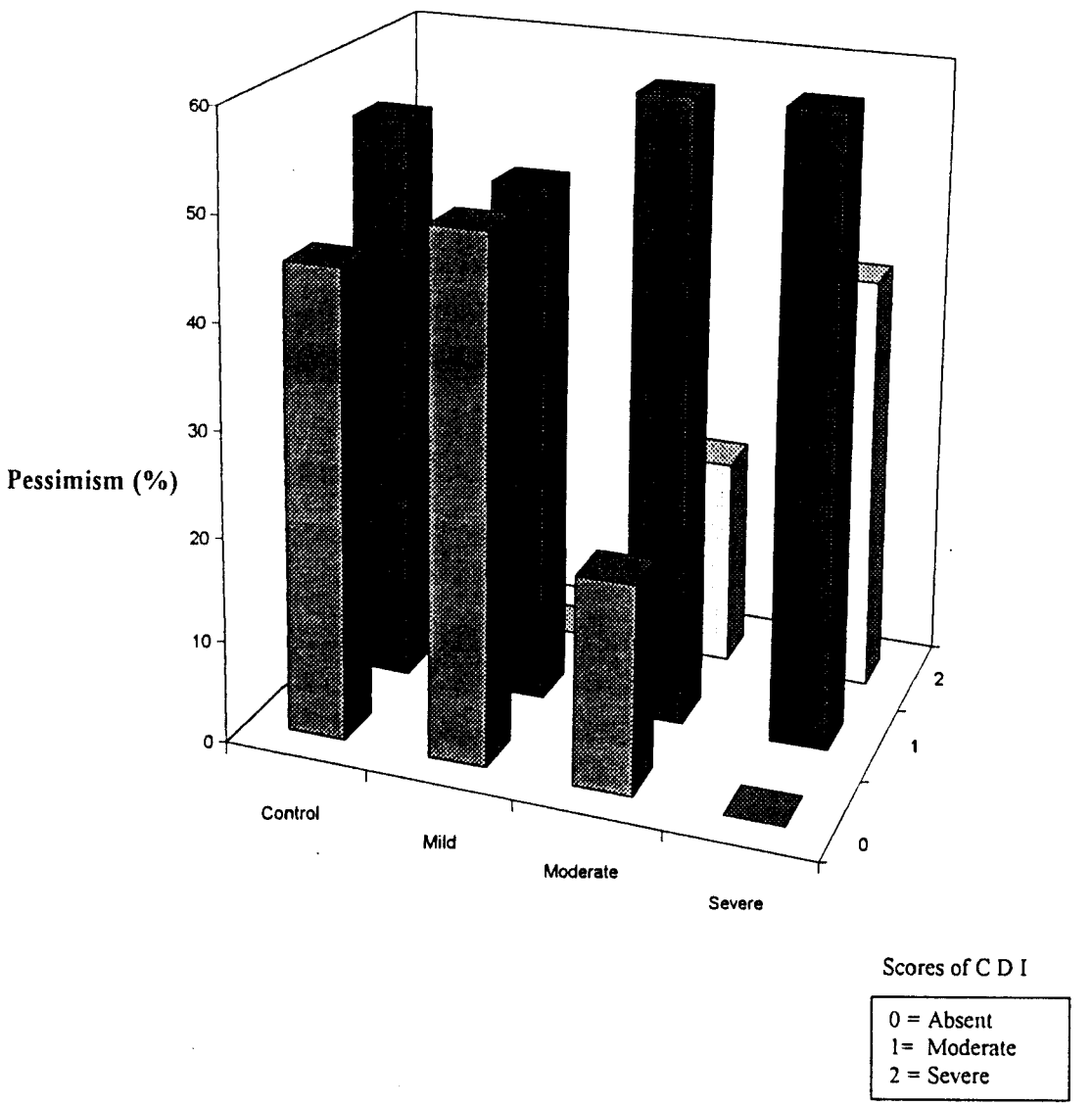
| | sIL-2R (pg/ml) in cases (no=60) | | |
|---|---|---|---|
| | R | P | Significance |
| Age | -0.18 | >0.05 | Insig. |
| SES | -0.16 | >0.05 | Insig. |
| Suicide | 0.23 | >0.05 | Insig. |
| Number of parents living with the child | 0.01 | >0.05 | Insig. |
| Maternal psychopathology | 0:1 | >0.05 | Insig. |

Insig = Insignificant

This table shows the correlation between sIL-2R and each of the age SES, suicide, number of parents living with the child, and maternal psychopathology has an insignificant relation.

Fig ( 5 )

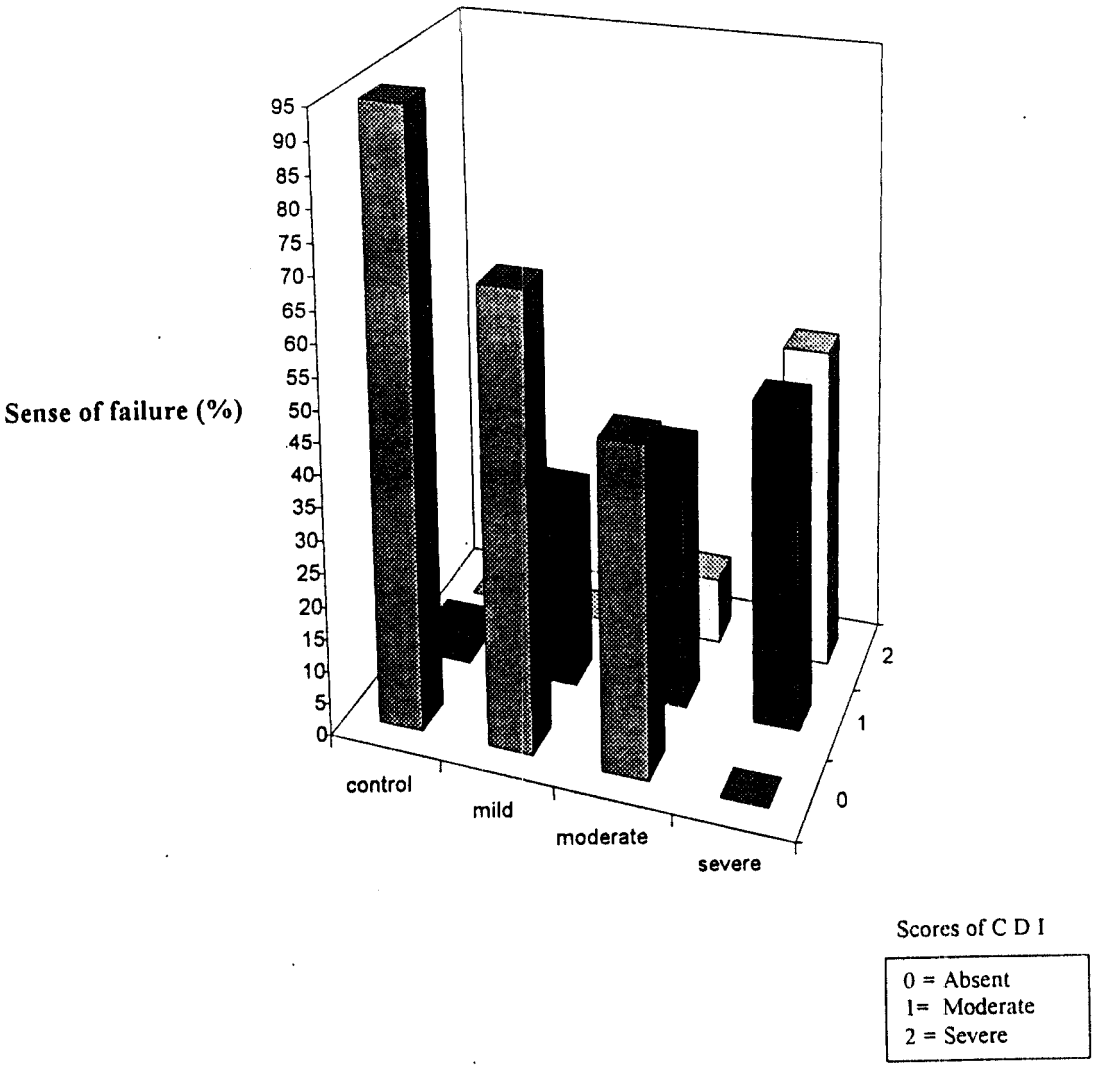
Pessimism in all groups of patients and control group .




C. D .I = Children Depression Inventory

Fig ( 6 )

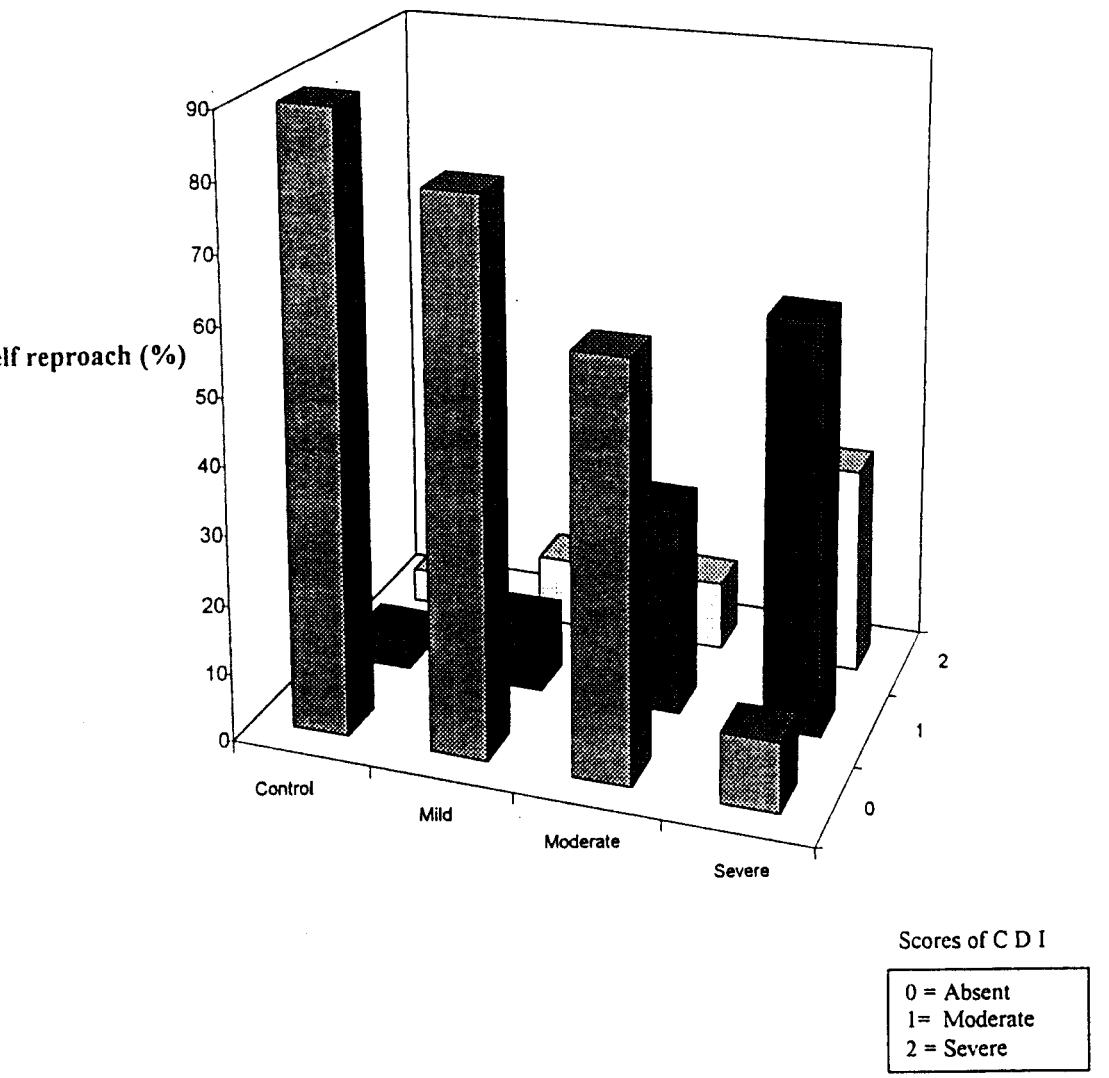
Sense of failure in all groups of patients and control group.




C. D .I = Children Depression Inventory

Fig ( 7 )

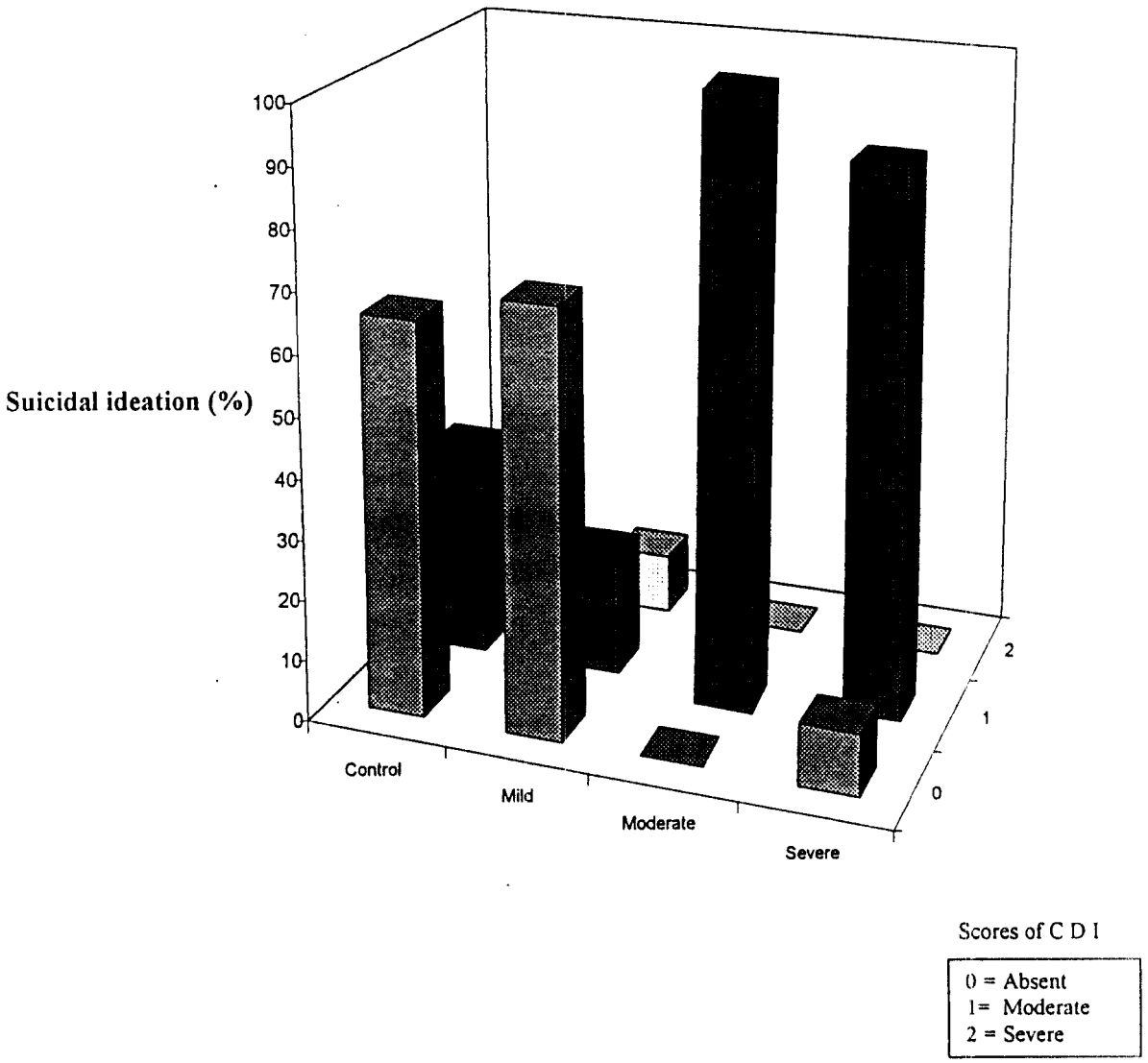
Self reproach in all groups of patients and control group .




C. D .I = Children Depression Inventory

Fig ( 8 )

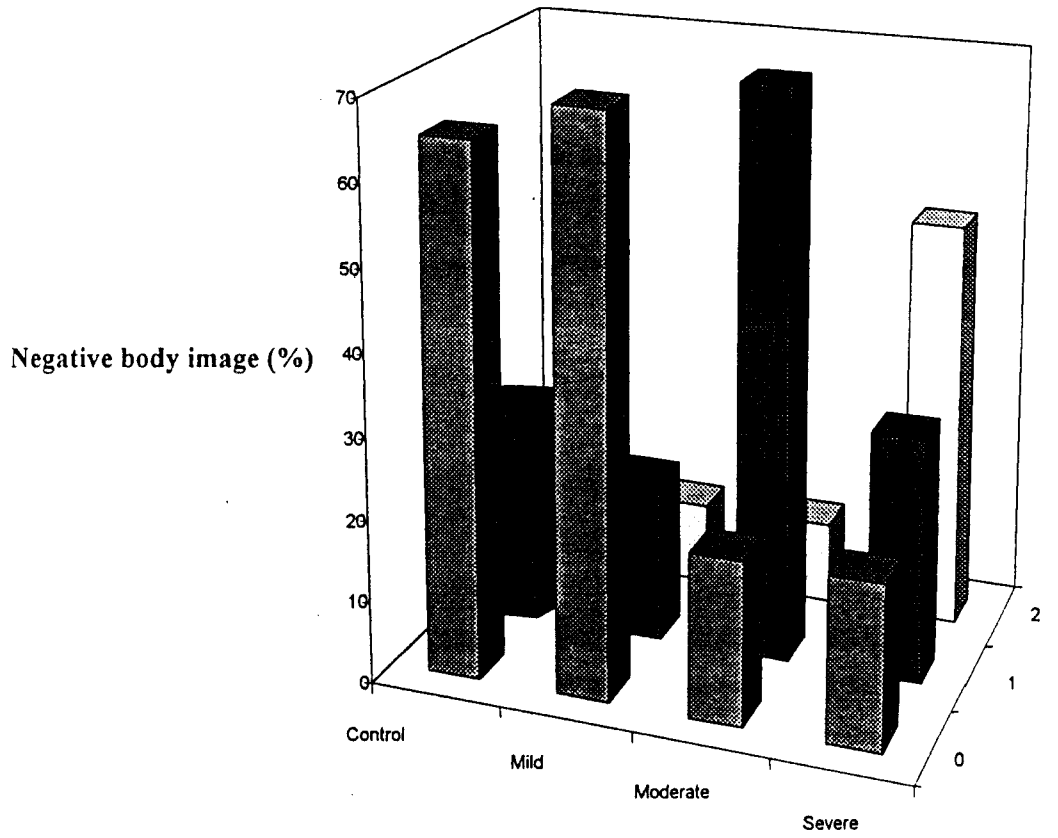
Suicidal ideation in all groups of patients and control group.




C. D .I = Children Depression Inventory

Fig ( 9 )

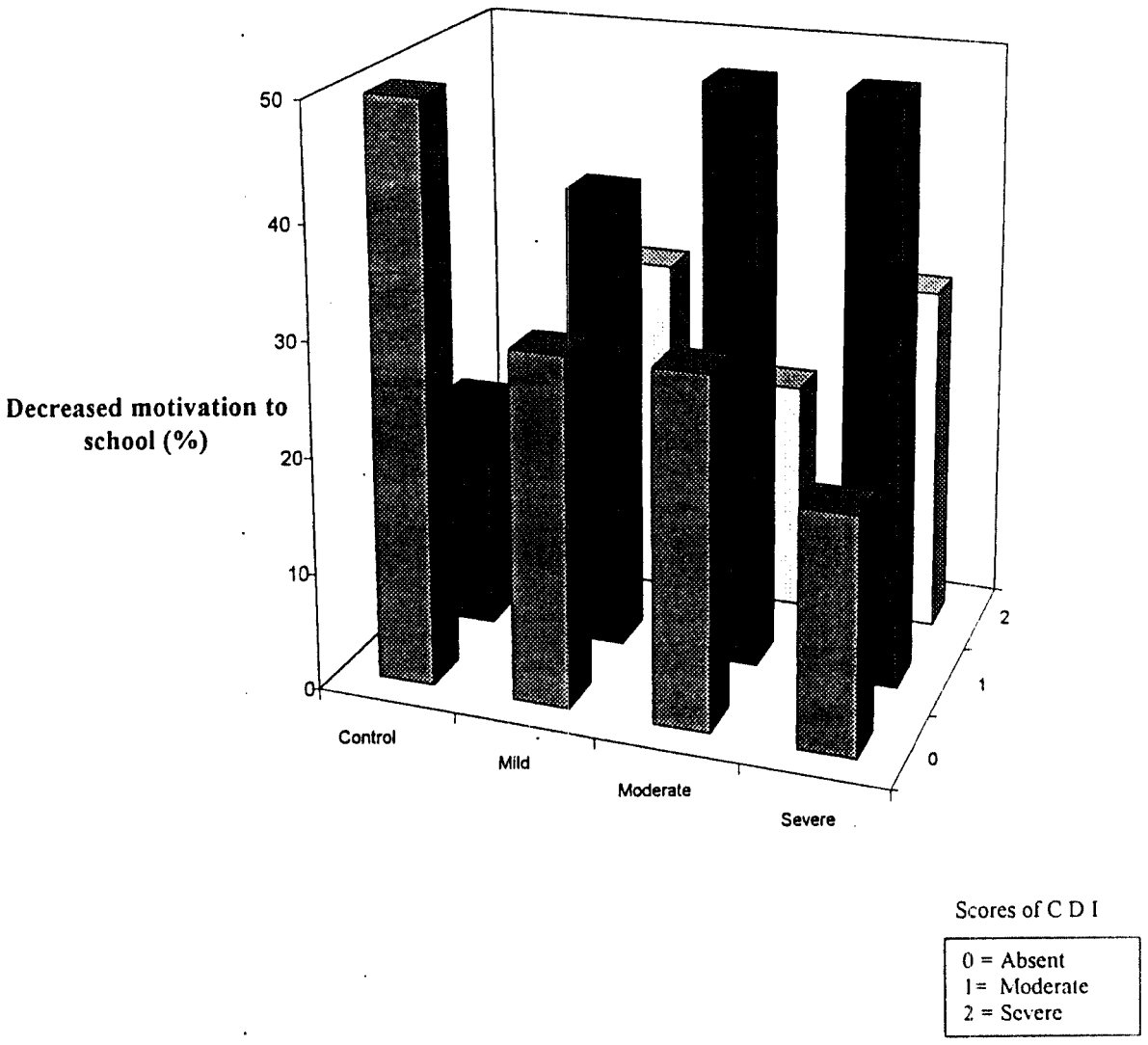
Negative body image in all groups of patients and control group.




C. D .I = Children Depression Inventory

Fig ( 10 )

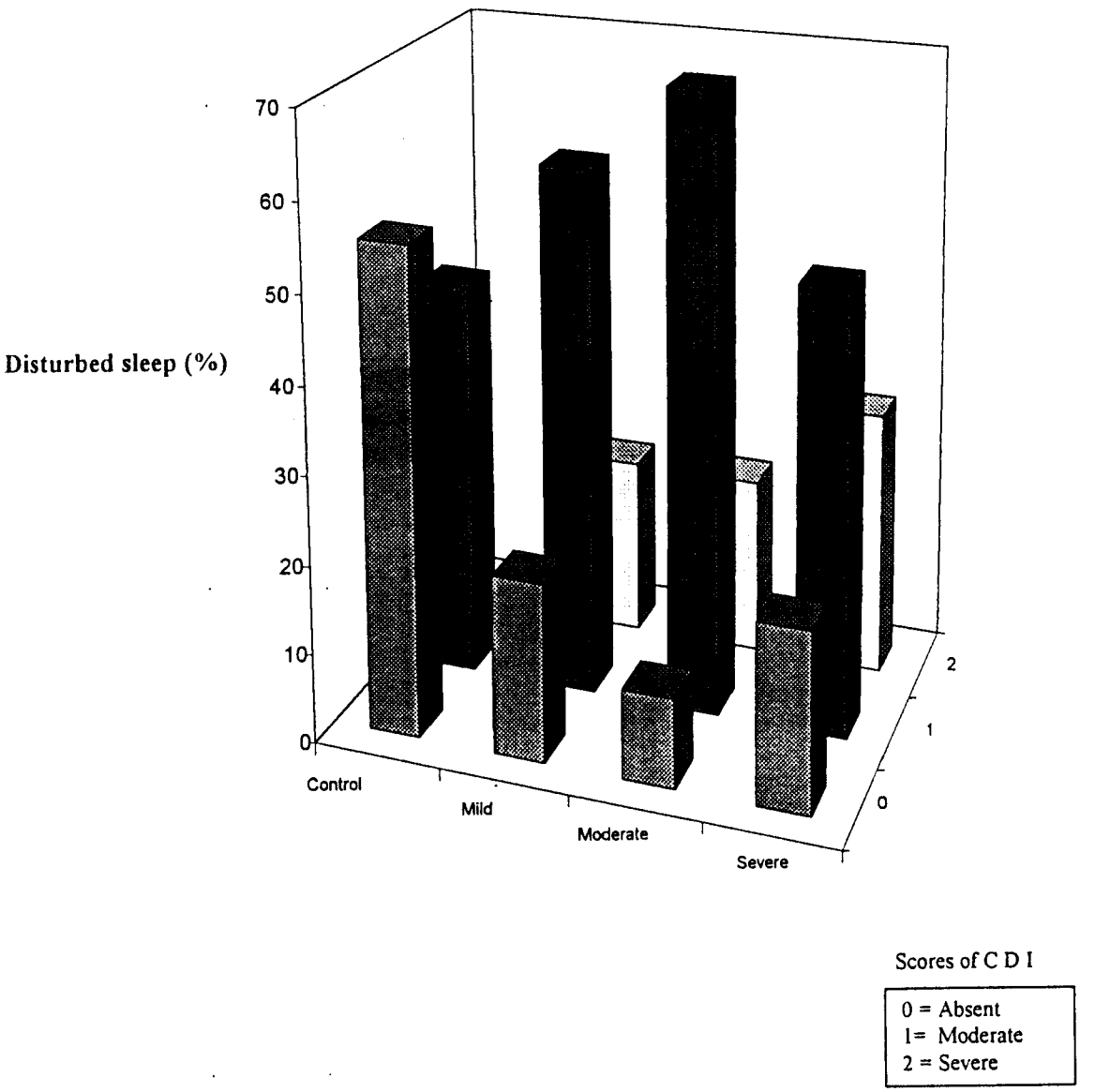
Decreased motivation to school in all groups of patients and control group.




C. D .I = Children Depression Inventory

Fig ( 11 )

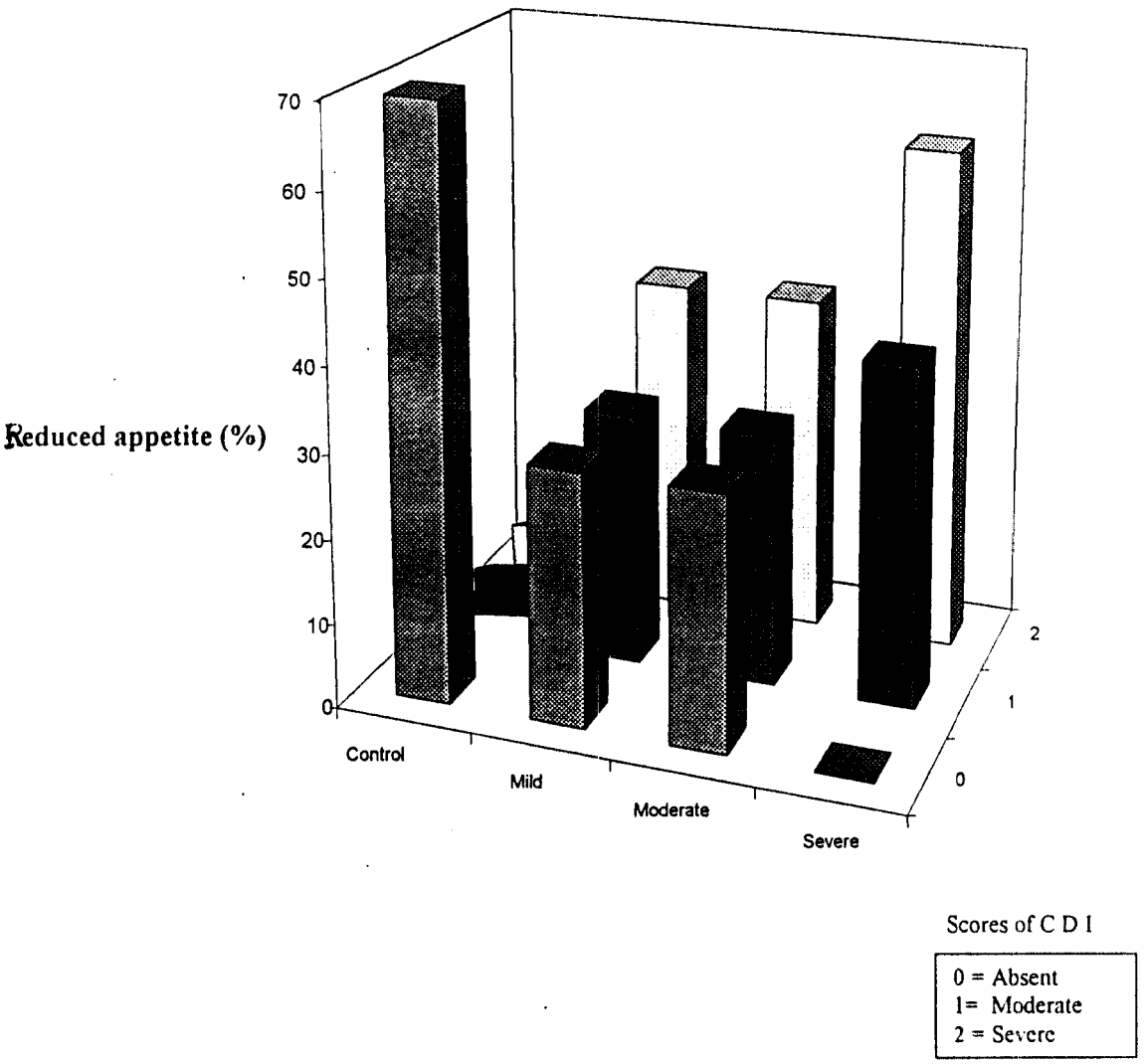
Disturbed sleep in all groups of patients and control group .




C. D .I = Children Depression Inventory

Fig ( 12 )

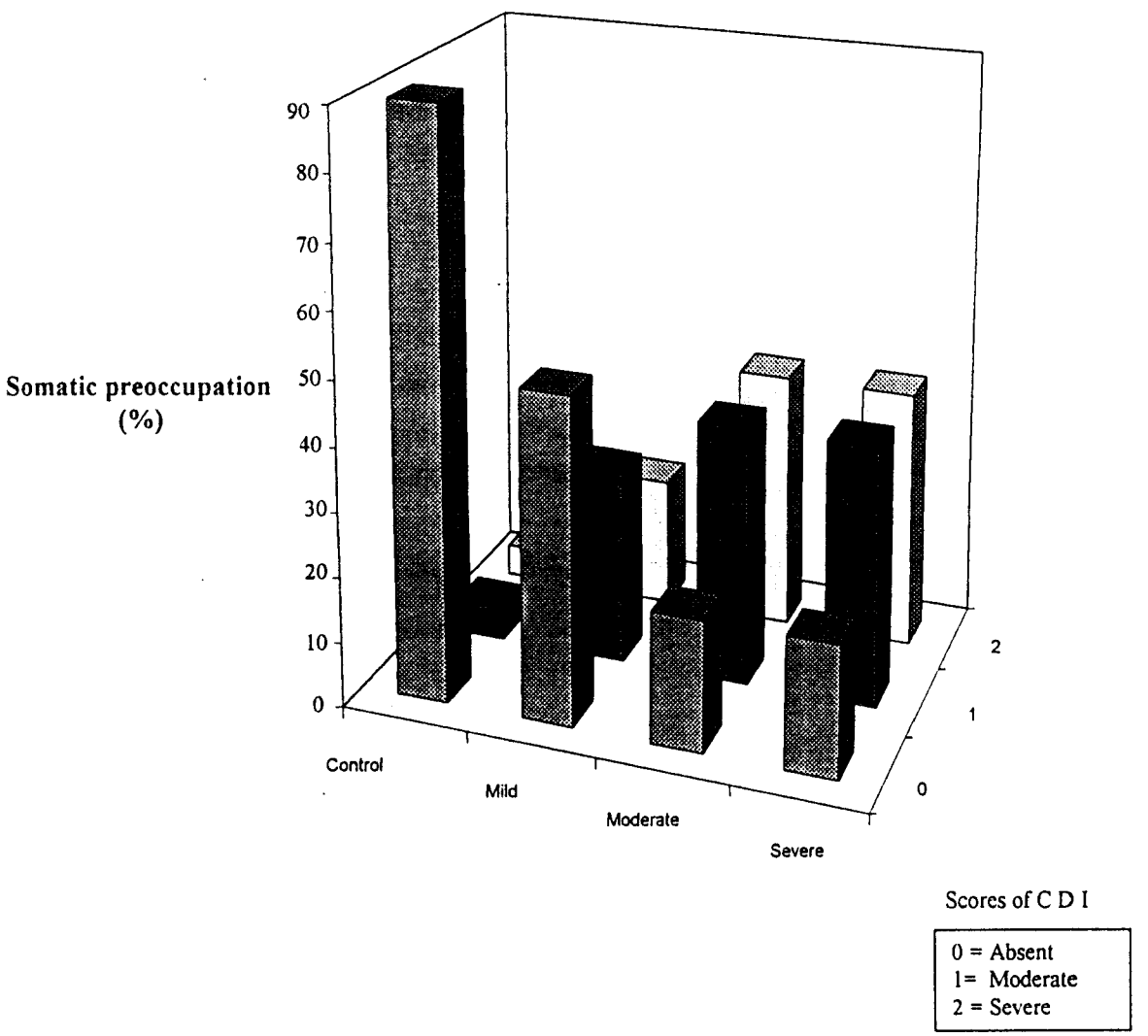
Reduced appetite in all groups of patients and control group .




C. D .I = Children Depression Inventory

Fig ( 13 )

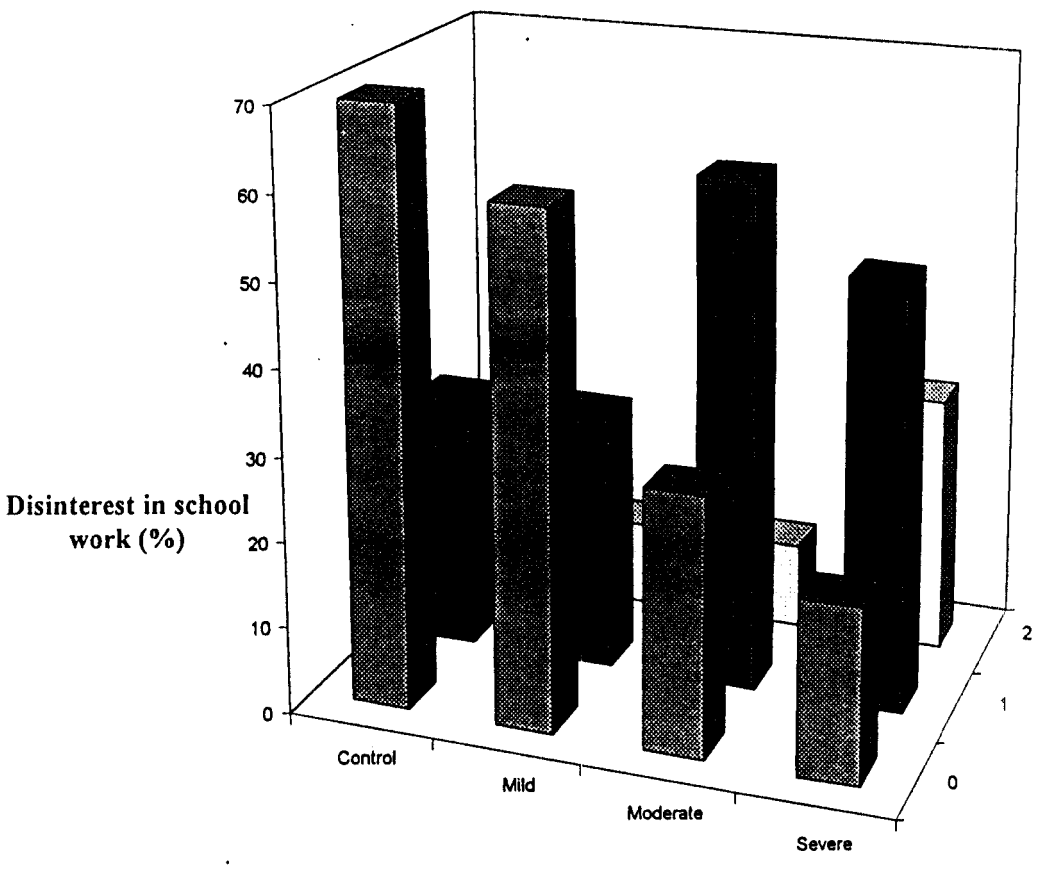
Somatic preoccupation in all groups of patients and control group.




C. D .I = Children Depression Inventory

Fig ( 14 )

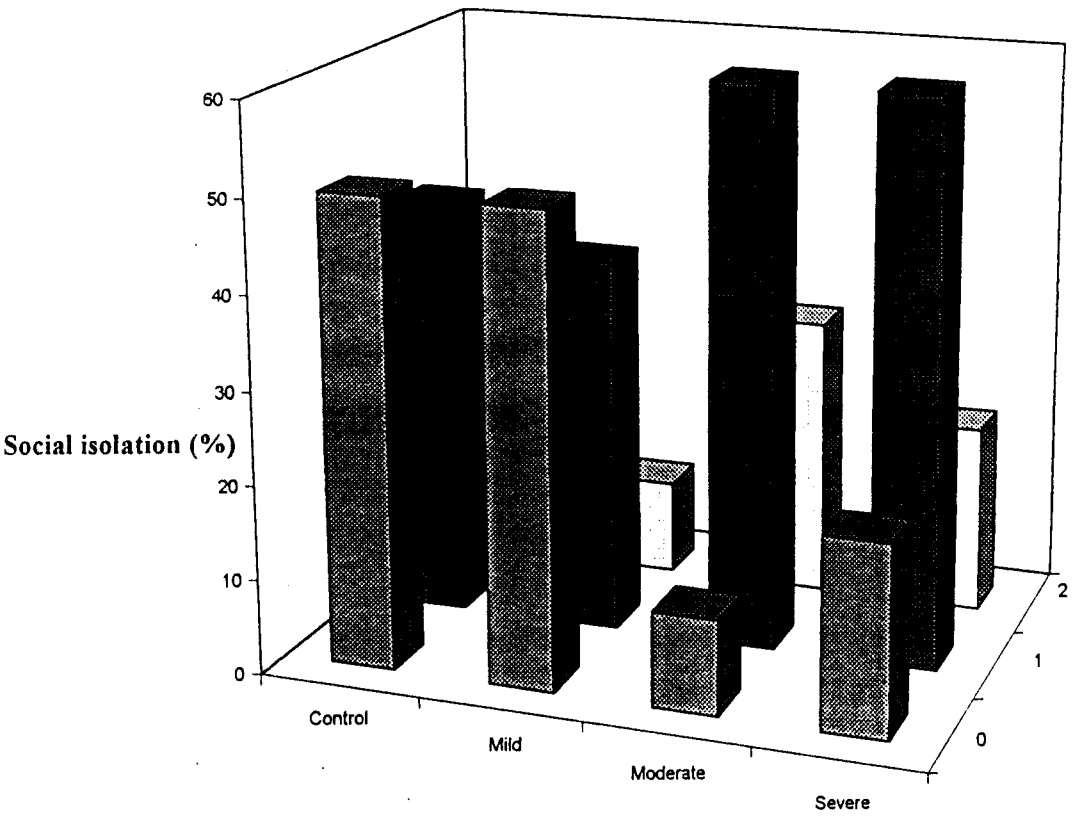
Disinterest in school work in all groups of patients and control group .




C. D .I = Children Depression Inventory

Fig ( 15 )

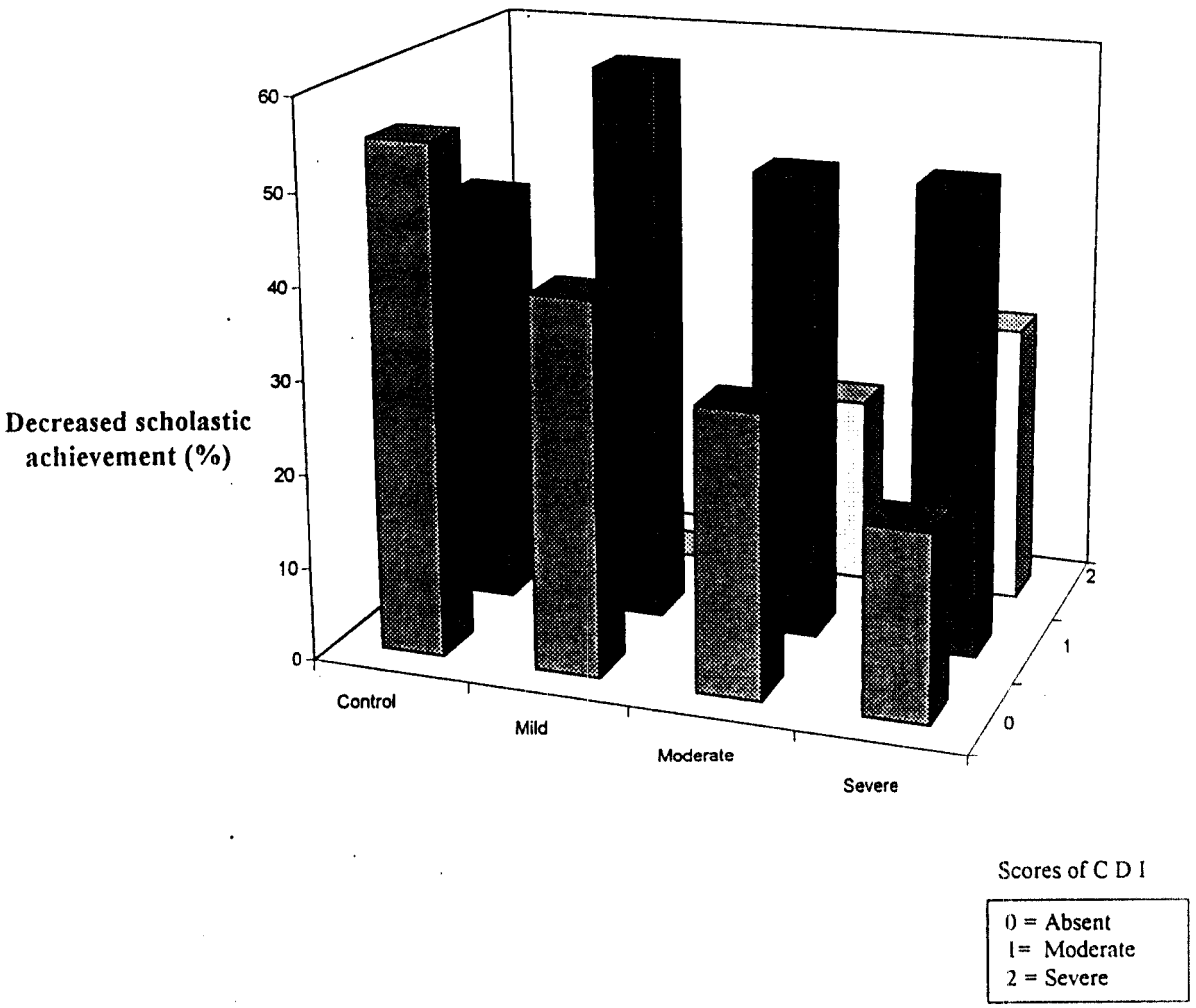
Social isolation in all groups of patients and control group.




C. D .I = Children Depression Inventory

Fig ( 16 )

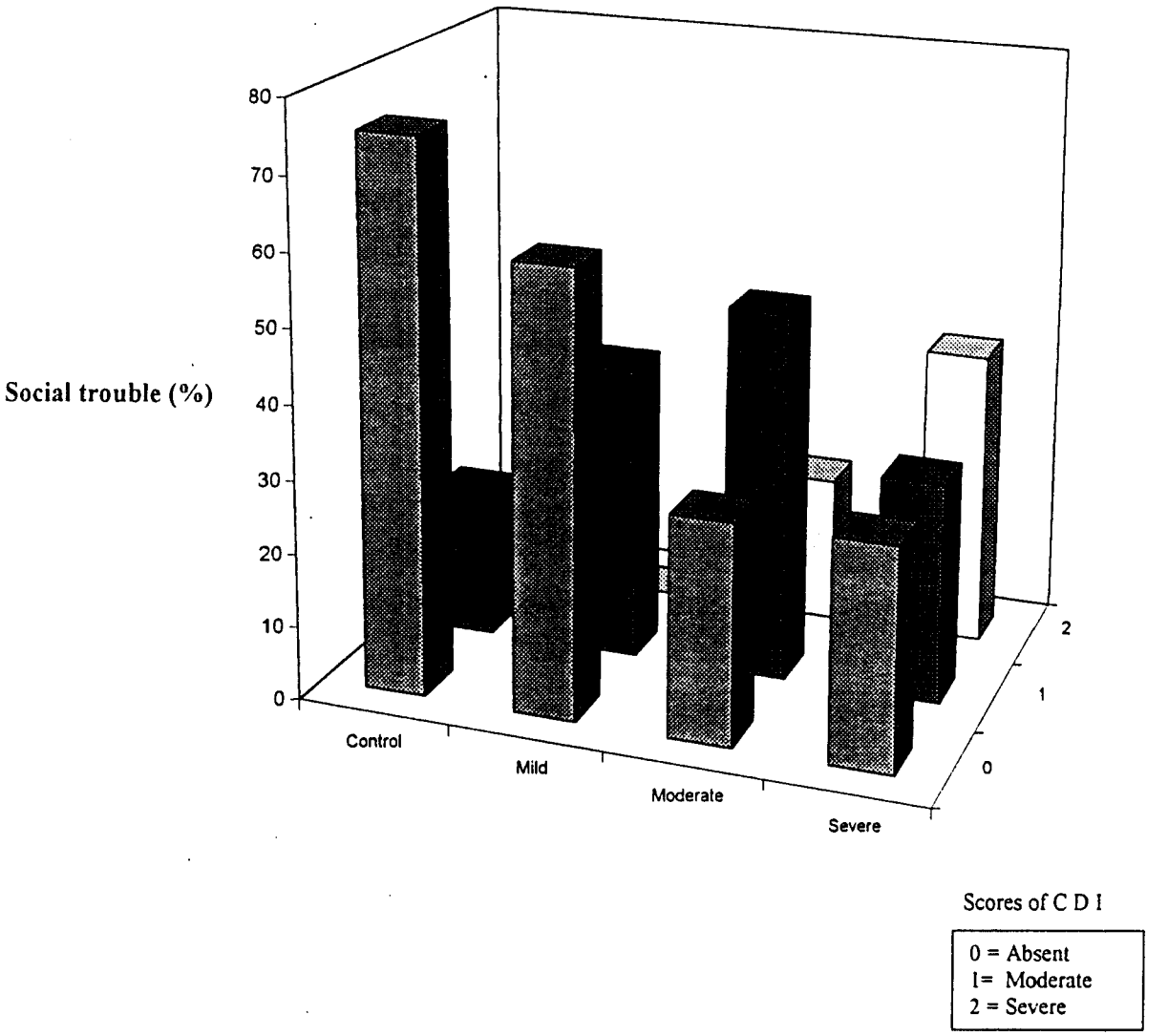
Decreased scholastic achievement in all groups of patients and control group.




C. D .I = Children Depression Inventory

Fig ( 17 )

Social trouble in all groups of patients and control group .




C. D .I = Children Depression Inventory

Fig ( 18 ):

Comparison between sIL-2R in control group and entire patient group.

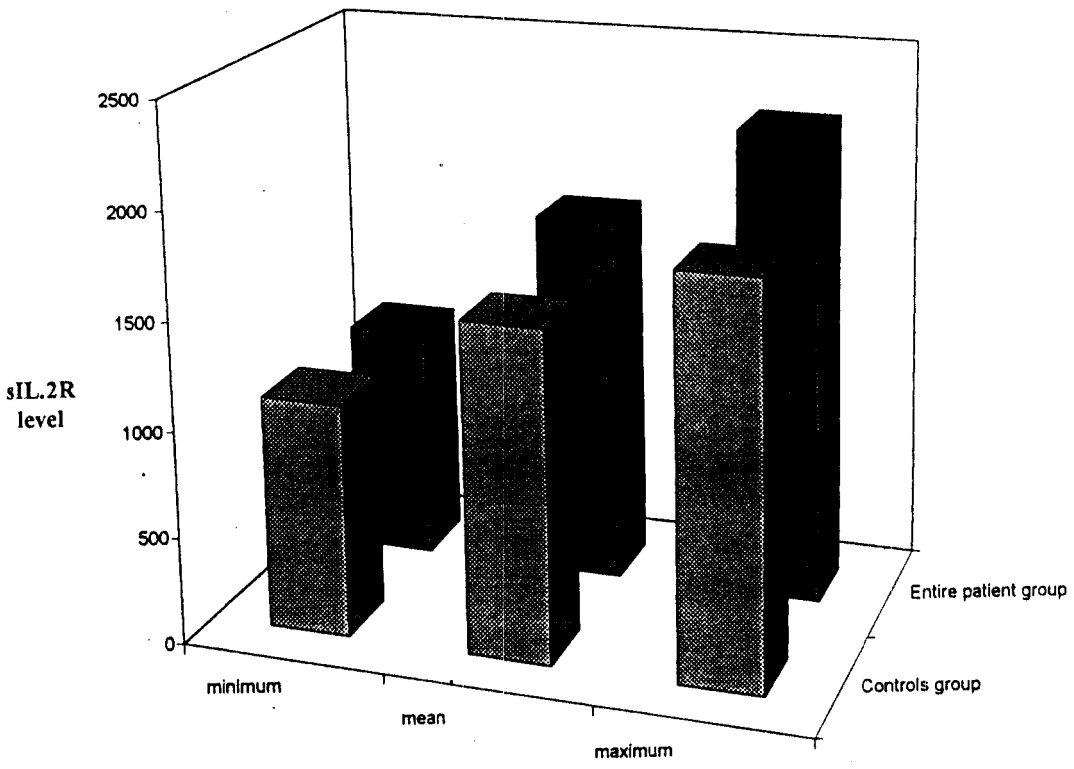
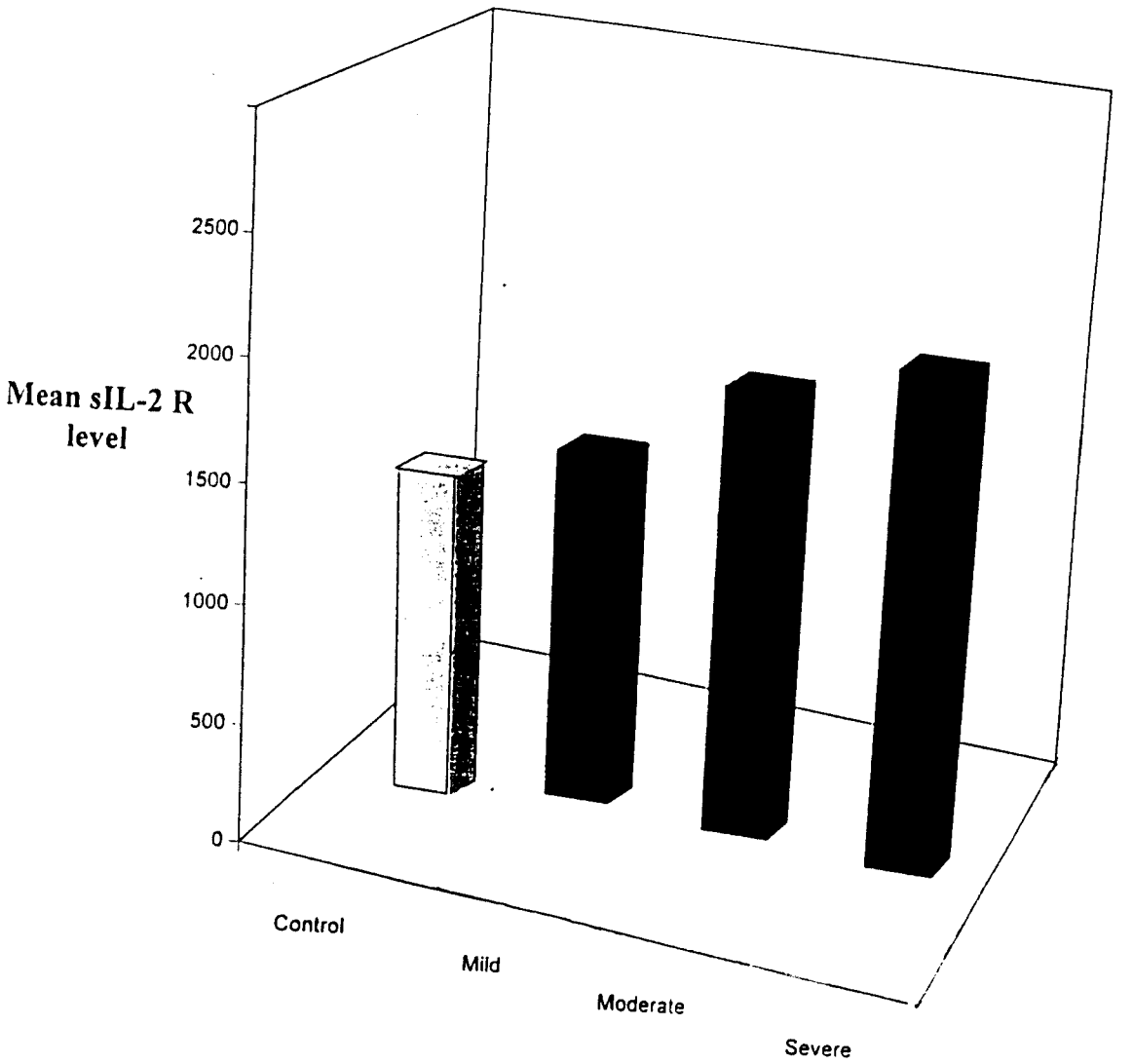


Fig ( 19 ) :

Distribution of sIL-2R in the whole groups of patients and control group.



# *Discussion*

# DISCUSSION

Depression represents a major public health problem. It is estimated that 13-20% of the population have some depressive symptoms at any given time and that about 5% of the population is assumed to suffer from major depression *(Licinio and Wong, 1999).* Two to seven percent of children and 3-10% of adolescents suffer from depression *(Eid, 1998).*

## Socio-demographic data

In this study, there was no significant difference between the age of the controls with mean value of 14.6 ± 3.6 years, and the entire depressive group with mean value of 14.53 ± 3.33 years. This is because we have intentionally selected children between the age of 7-18 years in all groups of patients and control *(Table 6).*

The researcher found that females were more than males (38 (63.3%) female: 22(36.7%) male). This goes with what other authors have found that females are more commonly affected than males especially with early onset depression i.e. in adolescent *(Leon et al., 1993, Cantwell, 1996, Bebbington, 1999).*

However some data point toward a trend for a closing of the gender difference in the incidence of depressive disorders for Childhood *(Weissman et al., 1993).*

***Trangkasombat and Likanapichitkul, (1997)*** found that major depressive disorder is equally present in females and males. Also ***Bebbinton, (1999)*** deduced that sex difference in depressive disorders is absent in childhood. There was a difference between these results and those of this study because the majority of cases in this study were in adolescent period (no.=46) (76%), while only 14 (23%) of depressed children were in childhood stage.

The mean of socio-economic status of cases is between average and above average (4.67±1.79), while that of control group is nearly above average (4.95±2.1), but there was no significant difference between them. This is because we have

chosen all groups of the same SES so as to match the control group with the sample group.

## Children's depression inventory (CDI):

Depression symptoms in children can be subtle and varied ***(Lamarine, 1995)***. In the current study dysphoric mood (sadness or irritability), loss of interest (anhedonia), and exhaustion were found in all depressed cases of this study (100%). This is because they are of the essential criteria of diagnosing depression by ICD-10 (1992) (on which the researcher diagnosis of episode of depression depends) in which two of these three items at least must be present to diagnose depression.

Sadness or irritability occurs in the whole depressive groups of this study (100%). This goes with what ***Elizabeth et al., (1996)*** reported that depressed children look sad, are tearful, have slow movements and monotone voice and speak in a hopeless and despairing manner. They describe themselves in negative terms, such as "I'm stupid" , "I'm a bad girl" and "no body loves me". Also ***Priest and Baldwin, (1992)*** stated that sadness and helplessness are prominent in young children. Also ***Montgomery (1990),*** announced that in depressed patients the commonest symptom is sadness, and it is a symptom which is usually recognized quite easily by the alert practitioner and that in severe cases it may not even seem necessary to ask about it, because it is so obvious from the facial expression and posture, and can be reliably measured by observation of behaviour or by assessment of what the patients say about themselves. ***Pozanski (1982)*** also reported the frequent occurrence of depressed appearance in younger children with MDD.

In this study anhedonia was one of the most common symptom in the whole depressive groups (100%). This is because the ability to take an interest and get pleasure from things seems to be one of the universal characteristics of healthy people and its loss is a sure indicator of ill health ***(Montgomery, 1990)***.

However, ***Carlson and Abbott, (1995)*** declared that anhedonia increases in frequency with age and careful questioning is needed to elicit even relative loss of interest and activity in children. But it was quite evident in the result of this study because CDI carefully questioned it and also because the majority of cases were in the adolescent period as already mentioned before.

Exhaustion which is one of the most common symptom in the whole depressive groups of this study (100%). This goes with what ***Roberts et al., (1995)*** stated that decreased energy occurs frequently in adolescent period. Also ***(Carlson and Abbott, 1995)*** confirmed that fatigue appeared to occur more frequently in the youngest populations.

Other important symptoms of maximum percent (100%) in the severe group of depression included: Pessimism, sense of failure and reduced appetite. Others with 90% included: Suicidal ideation, and self-reproach. Others with 80% were somatic preoccupation, loneliness and social isolation.

While in moderate group of depression other important symptoms: With 100% included: Suicidal ideation, and loneliness. With 90% included: Social isolation. With 80% included: Somatic symptoms and pessimism.

Pessimism (hopelessness, worthlessness) which was 100% in severe group, and 80% in moderate group of this study. It was easily recognized if the right questions are asked (***Montgomery, 1990***). Adolescents showed more hopelessness (***Ryan et al., 1987***). ***Priest and Baldwin (1992)***, and ***Montgomery and Asberg Scale (MADRS) (1979)*** found that one of the common clinical features of depressive illness is pessimistic thoughts. Also ***DSM-III (1980)***, and ***DSM-III R (1987)*** consider feeling of worthlessness as one of the common features of depression.

Sense of failure which is one of the commonest symptom of severe group of depression in this study (100%). It is a natural

consequence of pessimistic ideas (discussed before), and deterioration in school performance (discussed later).

Also ***Harrington (1993)*** considered that depressed people were characterized by a negative "cognitive set"; they have a negative view of themselves, the world, and the future. Thus they have intense feelings of personal inadequacy and a tendency to engage in self-depreciation. The patient may have a low opinion of himself and often believes that others take a depreciatory view of him.

Reduced appetite is one of the commonest symptom in severe group of depression of this study (100%). This goes with what ***El-Rashidi et al. (1993)*** declared that anorexia is a common presentation of illness in children. Also, ***Roberts et al. (1995)*** stated that in adolescents vegetative features such as loss of appetite, insomnia and decreased energy occur frequently. Also ***Carlson and Abbott (1995)*** found that symptoms like fatigue agitation and anorexia appeared to occur more frequently in the youngest populations.

Suicidal ideation was not only common in moderate group of depression (100%), but also in severe group of depression (90%) with insignificant difference between both groups ($P>0.05$). It is at least 8 times higher than that of the general population. Most persons who commit suicide have a mental disorder, with depression associated with about half of suicide. Although prepubertal children seemed to have just as much suicidal ideation as depressed adolescents, the potential lethality of their suicidal attempts was lower. They lack the cognitive ability to formulate successful suicidal plans. By contrast adolescents choose a more effective method such as gun shot ***(PDQ, 2000)***. In America the incidence of documented suicides by adolescents has tripled in the last 25 years, with 5.000 youths committing suicide each year and perhaps as many as 500.000-1.000.000 making an attempt ***(Kamerow, 2000)***. Prompt identification and treatment of depression is essential in lowering the risk of suicide ***(PDQ, 2000)***.

Loneliness was a symptom of maximum intensity in moderate (100%) and in severe (80%) groups of depression in this study. It might be a natural consequence of social withdrawal which was also high (90%) in moderate group, and (80%) in severe group of depression. This agreed with what ***Harrigton (1993)*** stated that social withdrawal was so common among depressed children and adolescents that consideration should be given to include it in the criteria for depressive disorder in this age group.

Guilt feelings (self reproach) was 90% in severe group of depression of this study. This is explained as follows; in Egypt, projected blame is commoner than guilt. However this projection or putting the blame (on God or sorcery) are only a mask for deeper seated guilt feelings ***(EL-Rashidi et al., 1993)***. However children, whose cognitive structure does not comprehend guilt as easily as adolescents and adults do, are less likely to have guilt feelings as a symptom ***(Carlson and Abbot, 1995)***. And that is why it is only highly significant in the severe group of this study.

Somatic symptoms were the common symptoms in severe (80%) and moderate (also 80%) subgroups of depressed cases of this study. This was in concordance with what ***Kammerow, (2000); & Elizabeth et al., (1996)*** who found that depressed persons frequently present with a variety of physical symptoms three times the number of somatic symptoms of controls, the most common being stomach aches and headaches. Also ***McCauley et al., (1991)*** reported a direct correlation between the frequency of somatic complaints and severity of depression in children. These findings are not strange because the body language is a common mode of expression in the Egyptian society ***(EL-Rashidi et al., 1993)***.

Also ***Elizabeth et al., (1996)*** stated that somatic complaints relate to depression in children over and above co-occuring anxiety disorder possibly because they are one of the ways a young child has of saying he or she does not feel well. Prepubertal children had more somatic complaints and

psychomotor agitation while adolescents had greater anhedonia and hypersomnia ***(Harrington, 1993)***.

If depression is not recognized, patients with somatic complaints may be subjected to the risks and costs of unnecessary diagnostic testing and treatment ***(Kamerow, 2000)***.

Functional impairment associated with a depressive syndrome in childhood extends to practically all areas of the child's psychosocial world: School performance and behavior, peer relationships, and family relations all suffer ***(Kaplan and Sadock, 1991)***.

In this study loss of interest and exhaustion were found in all groups of depressions as already mentioned before. Disturbed sleep (90% in moderate and 80% in severe group of depression). Disinterest in school and decreased scholastic achievement (are 80% in severe group). These symptoms showed significant difference between the group mentioned and the control group. However decreased motivation to school has insignificant difference between either moderate or severe group and control group (though it was 70% in moderate and 80% in severe group of depression). This might be due to the fact that all healthy children now dislike schools due to lack of enough vacations and increased sophistication of subjects and syllables.

School performance is invariably affected by a combination of difficulty in concentrating, slowed down thinking lack of interest and motivation, fatigue, sleepiness, depressive ruminations, and pre-occupations. Depression in child may be misdiagnosed as a learning disability. Learning problems secondary to depression, even when long standing, correct themselves rapidly after recovery from the depressive episodes ***(Kaplan and Sadock, 1991)***.

Occurrence of learning disabilities was determined in 30 inpatients children aged 6-12 with major depressive disorder. Learning disabilities occurred seven times more often compared to community base rates ***(Fristad et al., 1992)***.

Also ***Elizabeth et al. (1996)*** declared that depressed children's school performance deteriorates and all these agreed with the results of this study.

## Stressors and depression:

The current study showed that there was a highly significant difference ($P<0.01$) between cases and controls as regard the number of parents living with the child (0, 1 or 2).

Also ***Warner et al., (1995)*** stated that the omission of fathers is particularly serious because of strong evidence implicating parental influences on both normal and abnormal developmental processes.

***Abd El-Samei (1999)*** found that the majority of depressive episodes are provoked by severe events and marked difficulties. Some vulnerability factors add to the provocation as lacking a confinding relationship and loss of father below the age of eleven.

However, ***Kutcher and Marton (1994)*** suggest that parental loss in childhood is not by itself a sufficient explanation of the etiology of child/adolescent depression. Also the same authors do not support the hypothesis that insecure attachement leads to MDD.

This variability in results is not strange because this study was on Egyptian families where there is deep affection between the parents and the children. However Kutcher and Marton study in 1994 was on foreign children with different culture and where there is no coherence between the parents and their children that is why parental loss was not that important for the child who used to be alone even if his parents are living with him.

The results of this study on maternal psychopathology showed that there was a high significant difference between cases and controls as regard maternal psychopathology ($P<0.01$).

Elevated rates of mood disturbance in parents of depressed children potentially have both genetic and environmental implications ***(Cantwell, 1996)***.

*Also Cadoret et al., (1996)* results suggest that depression spectrum disease, has as one of its principal etiologic factors a gene environment interaction.

Having parents who are depressed may be a significant psychosocial and environmental stressor for the child. Having a depressed child may be a significant psychosocial stressor for parents *(Cantwell, 1996)*.

*Demerdash et al., (1995)* agreed that genes in the HLA region of chromosome 6 constitute one of the elements in the multifactorial etiology of affective disorder. *Todd and Heath (1996)* also assured the important genetic factors in the development of depression and anxiety disorders in youth.

*Farmer et al., (2000)* agreed that even when all susceptibility genes for depressive disorder have been identified, it will still not be possible to predict the development of disease with certainty until the relevant environmental risk factors have also been identified and the nature of the various interactions understood.

*Shiner et al., (1998)* found that only 18% of the mothers of the control adolescents had experienced major depression, whereas 47% of the mothers of depressed adolescents had experienced at least one episode. Previously obtained prevalence rates for major depression in first degree relatives of depressed youth have ranged from 20% *(Kutcher and Marton, 1991)*, to 54% *(Neuman et al., 1997)*. Also, *Mitchell et al., (1989)* specifically examined the prevalence of major depression in biological mothers and fathers of depressed children and adolescents and found that 56% of mothers and 34% of fathers had experienced major depression. These adolescents may have experienced more serious depression and thus may have been more likely to have relatives who had also experienced depression. It is also possible that depressed parents may be more likely to refer their children for treatment than non depressed parents. That is why perhaps rates obtained by *Mitchell et al., (1989)* may be higher.

*Dierker et al., (1999)* found that both the specific parental disorders and the number of affected parents seem to play an important role in child dysfunction.

## Relation between sIL-2R and depression:

It is a matter of debate whether depression is a cause or a consequence of abnormalities in immune functions including T cell activation. Some authors suggested that the etiology of depression may be related to immune activation for example by infectious agent. Others gave attention to immunological changes as a result of depression. It is also possible that a common factor may lead to both *(Smith, 1991)*.

In the present study, the sIL-2R circulating levels in serum were measured. They were found to be significantly increased in the depressed group of patients when compared to normal controls ($t=2.65$, $P<0.05$) *(Table 13, Fig, 18)*.

Also when severely depressed subgroup was compared to mildly depressed subgroup (using ANOVA test) or to control (using t test), the results were highly significant ($P<0.05$), and on comparing moderate group to control group (using T test) or mild group (using ANOVA test) results were highly significant ($P<0.005$). However on comparing the moderate with severe subgroups (using ANOVA test), and the control group with mild subgroup of depression (by T test) the result of both were insignificant ($T=0.66 >0.1$) *(Table,14 Fig,19)*.

The increased concentration of sIL-2R in the peripheral blood of depressed patients has been reported in other studies *(Maes et al., 1995; Sluzewska et al., 1996; and Khodair and Khalil, 2000)*.

*Allen Mersh et al., (1998)* found that there were significant positive correlation between serum sIL-2R alpha and hospital anxiety and depression (HAD) score, and that IL-2R alpha level was a significant independent predictor of HAD depression score.

*Irwin, (1999)* deduced that severity of melancholic symptoms appear to moderate the immune changes in depression.

The increase in T cell activation markers seems to be a series of immunological changes that is becoming more manifested along the course of the disease. ***Maes et al., (1995)*** proposed that the initial event in these transformation is the increased IL-1B production by monocytes. Recognition of antigen presented by the monocytic lineage and the necessary signals provided. by IL-1 may activate resting mature T cells. Activation may be accompanied by the appearance of the newly expressed class II MHC HLA DR molecules. The second phase of immune activation may occur during moderate stage of depression that the activated T cells may acquire IL-2R. (That is why the increase in IL-2R does not occur in the mild subgroup of patients). In the third phase, in severe depression activated IL-2 producing cells may promote proliferation of their own clones, other T cells and B cells with expression of Ig receptors.

***Maes et al., (1993)*** have reported that severe depresssion may be accompanied by a systemic immune activation with an increase in the number of T cells expressing activation receptors ($CD_7$+ $CD_{25}$+) and by the appearance of previously unexpressed T cell surface makers ($CD_2$+ HLADR+). ***Irwin (1999)*** also reported that depression appears to be associated with increase in at least one measure of immune activation.

***Muller and Ackenkeil (1998)*** explained the immune system activation associated with depression by the release of noradrenaline could act as a cytokine activating stimulant, through the release of IL-6, leading to immune phenomenon mediated by cytokine cascade.

***Abbas et al. (1999)*** explained that chronic T cell stimulation leads to shedding of IL-2Rα. Shed receptor proteins may bind free IL-2 preventing its interaction with target cells. However the much greater affinity of IL-2R βγc for IL-2 compared with IL-2 Rα alone suggests that serum IL-2Rα is no likely to contribute significantly to immunosuppression. Clinically, an increased level of shed IL-2Rα in the serum is a marker of strong antigenic stimulation.

On the other hand ***Bigot et al., (1999)*** deduced that patients with mood disorders are prone to increased risk for particular physical illnesses, neoplasms, .autoimmune disorders, bronchial asthma, and allergies. Also ***Johnson et al., (1999)*** deduced that depressive symptoms commonly follow severe bacterial or viral infections, even in hidden or unsuspected infections. The depression in acquired immune deficiency syndrome (AIDS) is explained by the fact that HIV infection of macrophages leads to their activation and increased cytokine secretion. ***Miller, (2000)*** demonstrated that a substantial subset of patients with depression exhibit persistent elevations in the glucocorticoid, cortisol. Glucocorticoids have been shown to inhibit T helper $(H)_1$ cytokine (IFNγ, TNFβ and IL-2) production while sparing $TH_2$ (IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13) responses. Corticosteroids have also been shown to induce production of TGFβ which in turn may inhibit the immune response ***(Cooke, 1998)***.

***Table (15)*** shows that relation between sIL-2R and age in all subgroups of patient and control group was nonsignificant. However ***Gotoh et al., (1999)*** deduced that mean sIL-2R concentrations in both serum and urine of children were significantly higher than those of adults and that their concentrations in children showed progressive decline to reach those of adults by the age of 15 years.

The discrepancy between the results might be due to the difference in age groups in both studies. Age in our sample was chosen between 7 and 18 years while in ***Gotoh et al. (1999)*** it was 1 to 67 years. Also ***Gotoh et al. (1999)*** study was carried out on Japanese people while our study on Egyptian, which may be a significant variable considering racial differences. Moreover, ***Gotoh et al. (1999)*** study was done on normal persons not diseased.

The relation between sIL-2R and sex in subgroups of patient and control revealed a highly significant difference only in case of severe subgroup ($t=0.97$, $P<0.01$) being higher in males (2118.75±49.6) versus females (1945.8±166.3). This agreed with what ***Miller (2000)*** claimed that patients who are severly

depressed, older and male have shown to be the most likely to show immune changes. This may be explained by what ***Haack et al. (1999)*** found that sIL-2R is significantly affected by smoking habits (which may be more in the severe depressed adolescent males than in any others group), and by other non pathological parameters such as exercise (though not expected to be found in severe depressed patients but is possible to be more in Egyptian males than Egyptian females) or it may be explained by other factors which needs further studies.

However ***Gotoh et al. (1999)*** deduced that there was no difference in the values of sIL-2R between males and females. This discrepancy may be due to the fact that Gotoh's study was conducted on healthy Japanese people between age of 1-67 years as already mentioned before.

However, ***Haack et al., (1999)*** found that sIL-2R were significantly affected by gender.

Also ***Olff (1999)*** noted that the relationship between depression and immunity is affected by gender.

It is by now widely recognized that acute and chronic stress have an impact on the immune system. Acute stress may have a stimulating effect on the immune system, while in the case of chornic stress, the immune system may be down-regulated. There is considerable individual variability in the immune response to stress. This seems to a large extent to be determined by the subject's way of dealing with stress ***(Olff, 1999)***. This may explain why in the researcher's study there was no significant difference between the sIL-2R level in depressed children living with no or one parent and those living with two parents, while in case of maternal psychopathology only in severe depressive group a significant difference was detected between depressed children with depressed mothers and depressed children with healthy mother (non depressed).

The perception and evaluation of a stressor and the specific ways of stress coping may in different ways be related to various aspects of stress response: sympathetic nervous system (SNS) activation and activation of the hypothalamic pituitary-adrenal

(HPA) axis, both systems affecting the immune system *(Olff, 1999)*.

*Watkin (1995)* assumed that psychosocial stress has been shown to turn on hypothalamic messenger ribonucic acid (m RNA) expression of cotricotropin releasing factor (CRF), preproenkephalin, and vasopressin in the hypothalamus, resulting in increased circulating levels of adrenocorticotrophic hormone (ACTH) and corticosterone.

*Sei et al. (1991)* declared that restraint stress suppressed the mitogen-induced rise in intracellular calcium in $CD_4^+$ cells but enhanced the rise in intracellular calcium in $CD_8^+$ cells. Conversely, chronic stress suppressed intracellular calcium in $CD_4^+$ cells but had no effect on intracellular calcium in $CD_8^+$ cells. The authors suggest that the differential effects of restraints stress on T lymphocyte subpopulations may be mediated by acute changes in corticosteroid levels.

However, *Zachariae et al. (1991)* studies on possible effects of emotion on immunity have found that the immunosuppressive effect of emotional depression and bereavement could not be linked with a corresponding rise in cortisol levels. Numerous substances other than the "classical stress hormones" such as cytokines were suggested to be responsible for the connection between emotional states and immunologically related processes. Measurement of sIL-2R in serum did not however, reveal any significant differences. A large number of peptides and other transmitter substances generated in the central nervous system may be involved in the central autonomic or blood-borne regulation of immune cells. The fact that white blood cells such as lymphocytes appear to possess receptors for agents synthesized in the nervous system such as serotonin, growth hormone, prolactin, acetylcholine, endorphins, encephalins, and substance p, has lead some to argue that neuropeptides and their receptors may be the key to the understanding of the biochemistry of emotion as well as the links between mind emotion and immunity.

Sleep disturbance appear to moderate the immune changes in depression, but the biological mechanisms that account for the

link between these neurovegetative sympotms and depression are not yet known ***(Irwin, 1999)***. Also ***Miller, (2000)*** suggests that sleep disturbance may be an especially important factor in this regard. However the researcher work failed to show any significant difference between sIL-2R levels in depressive group with score zero sleep disorder in children depression inventory (CDI) and depressive group with score one or two sleep disorder together. However, on comparing score 0 alone to score 2 alone a significant difference was detected in the level of sIL-2R ($P<0.05$) using ANOVA test Table (23).

***Nassberger and Traskman Bendz (1993)*** found a median sIL-2R concentration far above the range of healthy controls in plasma samples from medication-free suicide attempts with mood disorder. No sex differences and no differences between diagnostic and suicidal subgroups were noted. In follow up samples, the sIL-2R remained at high levels. Furthermore sIL-2R seems to be independent of drug therapy.

However, the results failed to show any significant corelation between suicide and sIL-2R ($P>0.05$) as no one attempted suicide but all of them had suicidal thoughts (ideations) (they wish to be dead but not able to do so).

Correlations between sIL-2R and each of age, socioeconomic status (SES), suicide, number of parents living with the child, and maternal psychopathology in all subgroups of patients and control revealed insignificant correlations. This may be due to small size of the sample, and few numbers of the scores in the majority of items e.g. suicide number of parents living with the child and maternal psychpathology.

However, ***Olff (1999)*** noted that the relationship between depression and immunity is affected by personal resoureces, and that increasing the subjects abilities to cope with stress and to reduce the negative affect by psychological interventions may on the other hand have a beneficial effect on the immune system.

# *Summary and Conclusion*

# *Summary*

Depression may be comorbid, disabling syndrome that affects approximately 2-7% of childhood, 3-10% of adolescents. Some researchers reported that depression is accompanied by in vitro immune-suppression as indicated by lymphocyte transformation tests, lower number of T and B cells and diminished natural killer cell activity. Others reported that depression is characterized by T-cell activation which is manifested by increased activated –T lymphocytes, interleukin-2 receptors bearing cells, and human leukocyte antigen (HLA) DR+T cells and increased level of soluble interleukin-2 receptor.

The aim of the study is to investigate the most common symptomatology in different categories of depression (mild, moderate, and severe). It also aimed to study interleukin-2 receptors in depressed children according to the various degrees of severity of the disorder.

A sample of 60 Egyptian patients with an age between 7-18 years experiencing an episode of depression were selected from the institute of psychiatry, Faculty of medicine, Ain Shams University by ***ICD-10, (1992)***.

Patients were subclassified into 3 groups according to the severity of depression into mild, moderate and severe subgroups of depression by ***ICD-10, (1992)***.

Cases and controls (80) were subjected to: psychiatric interview (to pick up cases and control), complete physical examination (to exclude any concomitant physical illness), a self-rating questionnaire (Egyptian version of the children's depression inventory CDI) ***(Abdel Fattah, 1998)*** applied to all the sample children to detect unrecognized depressive symptoms and to have scores for each symptoms to be able to do correlation between any symptom and sIL-2R.

A questionnaire for socioeconomic level ***(EL-Shakhs, 1995)*** was applied to parents of the children of both cases and controls, to assure that they are of the same socioeconomic level.

Finally serum was used for detection of soluble IL-2R using enzyme linked immunosorbent assay (ELISA).

The results were statistically analyzed using the mean, standard deviation, T-test, chi-square, ANOVA test, and correlation coefficient.

The prevalence of depression in females was found to be commoner than male [Female (63.3%) and male (36.7%)]. With a high significant difference between them.

The mean value of socio-economic level of the parents of the children was found to be between average and above average.

Sadness, loss of interest and exhaustion were found in all depressed cases of this study (100%). Other important symptoms in severe group of depression: With 100% included: Pessimism, sense of failure, and reduced appetite. With 90% included: Suicidal ideation and self reproach. With 80% included: Somatic preoccupation, loneliness, and social isolation. While in moderate group other important symptoms: With 100% included: suicidal ideation and loneliness. With 90% included: Social isolation. With 80% included: Somatic symptoms and pessimism.

Disinterest in school and decreased scholastic achievement (both were 80% in severe group). Both symptoms show high significant difference between the severe group and the control group. On the other hand decreased motivation to school was shown to have insignificant difference (though it was 70% moderate and 80% in severe groups of depression). There was a high significant difference between the loss of one parent or two parents in cases and controls ($P<0.01$), also between maternal psychopathology in cases and controls ($P<0.01$).

The soluble interleukin-2 receptors (sIL-2R) levels in serum were found to be significantly increased in the depressed group of patients when compared to controls ($T=2.65$, $P<0.05$). Also on comparing either severe or moderate depressed subgroups to either mild subgroup of depression or control group the result was always highly significant. However, on comparing the moderate to severe subgroups of depression and the control

group to mild subgroup of depression the result of both were insignificant (P>0.1).

The mean serum level of sIL-2R was higher in males (211.78±49.6) than females (1945.8±166.3) in severe subgroup of depression with a high significant difference between both only in severe group.

The level of mean sIL-2R in the severe group of depression with maternal psycho-pathology is lower than the same group (i.e. severe) with no maternal psychopathology with a significant difference between both.

The level of mean sIL-2R detected in patients with severe complains of disturbed sleep is lower that of patients with no sleep disturbance with significant difference between both.

Lastly in this study effects of socioeconomic status of the parents of the child, age of the child, number of parents living with the child, maternal psychopathology and suicidal ideation had no role on the levels of sIL-2R of the child, because there was no significant correlation between cases and controls as regard these items.

# *Conclusion*

In the present study cases were chosen between the age of 7-18 years with mean age 14.5 years. Female sex was more common than male. Socio-economic standard between average and above average. The general pattern of the results lead to the following conclusions:

1. Sadness, loss of interest and exhaustion were found in all depressed cases of this study.
2. The most common C.D.I items (100%) in severe group of depression are: Pessimism, sense of failure and reduced appetite. Suicidal ideations and self reproach are 90% in severe group. Somatic preoccupation, loneliness and social isolation are 80%. While in moderate group of depression: Suicidal ideations and loneliness are 100%. Social isolation is 90%. Somatic symptoms and pessimism are 80%.
3. Disinterest in school and decreased scholastic achievement are 80% in severe group. Both symptoms show high significant difference between the severe group and control group. On the other hand decreased motivation to school is shown to have insignificant difference (though its 70% in moderate and 80% in severe group).
4. Loss of one or 2 parents, and maternal psychopathology increase susceptibility of depression in children.
5. As regards sIL-2R level in the serum, it is increased in depressed patients and is positively related to the severity of depression.
6. Soluble IL-2R is significantly positively related also to male sex only in severe depression, and it is insignificantly related to any sex in control group.
7. Maternal psychopathology significantly affects the levels of sIL-2R only in severe depressive group.
8. There is significant effect of severe sleep disturbance on the level of sIL-2R.

# *Recommendations*

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1- Setting reference values for sIL-2R.

2- Early treatment of depression in patients with immunologic disorders may improve disease outcome.

3- The use of serum sIL-2R as one of the markers of the severe and moderate category of depression.

4- Further studies are needed to know why sIL-2R is more in males with severe depression than females.

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# *Appendix*

## Raw data of age in the whole group of patients and controls

| no | Mild | Moderate | Severe | Control |
|---|---|---|---|---|
| 1 | 17 | 13 | 9 | 10 |
| 2 | 18 | 14 | 16 | 8 |
| 3 | 16 | 12 | 13 | 9 |
| 4 | 18 | 15 | 9 | 8 |
| 5 | 13 | 10 | 10 | 18 |
| 6 | 14 | 13 | 15 | 10 |
| 7 | 14 | 18 | 18 | 18 |
| 8 | 7 | 17 | 18 | 17 |
| 9 | 17 | 18 | 18 | 16 |
| 10 | 10 | 18 | 18 | 15 |
| 11 | 17 | 13 | 9 | 17 |
| 12 | 10 | 18 | 18 | 18 |
| 13 | 16 | 12 | 13 | 14 |
| 14 | 17 | 18 | 18 | 17 |
| 15 | 13 | 10 | 10 | 16 |
| 16 | 7 | 17 | 18 | 18 |
| 17 | 14 | 18 | 18 | 16 |
| 18 | 14 | 13 | 15 | 15 |
| 19 | 18 | 15 | 9 | 18 |
| 20 | 18 | 14 | 16 | 14 |

## Raw data of socioeconomic status (SES) in the whole group of patients and controls

| no | Mild | Moderate | Severe | Control |
|---|---|---|---|---|
| 1 | 6 | 4 | 1 | 2 |
| 2 | 7 | 5 | 5 | 1 |
| 3 | 6 | 7 | 6 | 6 |
| 4 | 5 | 7 | 4 | 6 |
| 5 | 1 | 7 | 4 | 3 |
| 6 | 6 | 2 | 5 | 5 |
| 7 | 2 | 4 | 4 | 1 |
| 8 | 7 | 4 | 6 | 7 |
| 9 | 6 | 4 | 4 | 6 |
| 10 | 2 | 6 | 3 | 6 |
| 11 | 6 | 4 | 6 | 6 |
| 12 | 2 | 6 | 3 | 7 |
| 13 | 6 | 7 | 5 | 6 |
| 14 | 6 | 4 | 4 | 5 |
| 15 | 1 | 7 | 4 | 6 |
| 16 | 7 | 4 | 6 | 1 |
| 17 | 2 | 4 | 4 | 6 |
| 18 | 6 | 2 | 5 | 6 |
| 19 | 5 | 7 | 4 | 7 |
| 20 | 7 | 5 | 1 | 6 |

***Scores of SES***

1= Very low
2= Low
3= Below average
4= Average
5= Above average
6= High
7= Very high

## Raw data of soluble IL-2R in the different subgroups of patients and controls

| no | Mild | Moderate | Severe | Control |
|---|---|---|---|---|
| 1 | 1425 | 1380 | 2180 | 1800 |
| 2 | 1185 | 2200 | 2180 | 1815 |
| 3 | 1530 | 1800 | 1995 | 1800 |
| 4 | 1680 | 1800 | 2100 | 1790 |
| 5 | 1995 | 2130 | 1860 | 1380 |
| 6 | 1470 | 1750 | 1800 | 1095 |
| 7 | 1680 | 1810 | 2100 | 1425 |
| 8 | 1400 | 2100 | 1740 | 1095 |
| 9 | 1710 | 2190 | 2055 | 1500 |
| 10 | 1785 | 2100 | 2140 | 1530 |
| 11 | 1425 | 1380 | 2180 | 1810 |
| 12 | 1785 | 2100 | 2140 | 1410 |
| 13 | 1530 | 1800 | 1995 | 1320 |
| 14 | 1710 | 2190 | 2055 | 1805 |
| 15 | 1995 | 2130 | 1860 | 1125 |
| 16 | 1400 | 2100 | 1740 | 1445 |
| 17 | 1680 | 1810 | 2100 | 1495 |
| 18 | 1470 | 1750 | 1800 | 1525 |
| 19 | 1680 | 1800 | 2100 | 1845 |
| 20 | 1185 | 2200 | 2180 | 1710 |

**Raw data of children depression inventory (CDI) in the whole groups of patients and controls.**

| no | Mild | Moderate | Severe | Control |
|---|---|---|---|---|
| 1 | 16 | 25 | 33 | 6 |
| 2 | 19 | 23 | 24 | 10 |
| 3 | 23 | 21 | 45 | 7 |
| 4 | 17 | 17 | 30 | 7 |
| 5 | 16 | 18 | 27 | 11 |
| 6 | 16 | 23 | 44 | 12 |
| 7 | 16 | 28 | 42 | 6 |
| 8 | 16 | 34 | 37 | 11 |
| 9 | 16 | 35 | 40 | 8 |
| 10 | 16 | 32 | 44 | 7 |
| 11 | 16 | 25 | 33 | 11 |
| 12 | 16 | 32 | 44 | 6 |
| 13 | 23 | 21 | 45 | 7 |
| 14 | 16 | 35 | 40 | 11 |
| 15 | 16 | 18 | 27 | 12 |
| 16 | 16 | 34 | 37 | 6 |
| 17 | 16 | 28 | 42 | 8 |
| 18 | 16 | 23 | 44 | 7 |
| 19 | 17 | 17 | 30 | 4 |
| 20 | 19 | 23 | 24 | 5 |

# *Appendix*

# المقياس المعدل للمستوى الإجتماعى/الأقتصادى للأسرة المصرية المعدل

إعداد

أ.د. عبد العزيز السيد الشخص

## أستمارة جمع بيانات
## عن الحالة الإجتماعية / الأقتصادية للأسرة

١- أسم الطالب: ..... المدرسة: .....

٢- وظيفة رب الأسرة أو مهنته بالتفصيل: .....

٣- المرتب الشهرى: .....

٤- مستوى تعليم رب الأسرة (أعلى مؤهل دراسى حصل عليه): .....

٥- وظيفة ربة الأسرة أو مهنتها بالتفصيل: .....

٦- المرتب الشهرى لربة الأسرة: .....

٧- مستوى تعليم ربة الأسرة (أعلى مؤهل دراسى حصلت عليه): .....

٨- مصادر أخرى لدخل الأسرة: .....

٩- قيمة الدخل من تلك المصادر: .....

١٠- عدد أفراد الأسرة: .....

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* تحاط هذه الاستمارة بالسرية التامة ، ولا تستخدم الا لأغراض البحث العلمى فقط.

جامعة عين شمس
معهد الدراسات العليا للطفولة
قسم دراسات طبية

# مقياس (د) للصغار- CDI - الصورة الفصحى

الاسم: الفصل:
تاريخ اليوم: المدرسة:
السن: الجنس:

عزيزى ...

أحيانا يشعر الصغار والشباب ببعض المشاعر ويفكروا فى بعض الافكار ، وفى هذه الكراسة بعض المشاعر والافكار مكتوبة فى صورة مجموعات ، تتكون كل مجموعة من ثلاث عبارات عليك أن تختار واحدة من كل مجموعة من العبارات ترى أنها تصفك خلال الاسبوعين الأخيرين، ثم قم بوضع علامة √فى المربع المجاور للعبارة التى إخترتها، وبعد ذلك إنتقل الى مجموعة العبارات التالية لها، وهكذا حتى تنتهى من كل المجموعات.

ويجب أن تلاحظ أنه لاتوجد إجابة صحيحة أو إجابة خاطئة ولكن المطلوب منك أن تختار عبارة واحدة من كل مجموعة ، وتكون هذه العبارة هى التى ترى أنها تصف حالتك خلال الأسبوعين الأخيرين بما فى ذلك اليوم وعلى سبيل المثال أنظر المثال التالى:

| | |
|---|---|
| | أنا أقرأ الكتب طوال الوقت. |
| | أنا أقرأ الكتب أحيانا. |
| | أنا لم أقرأ كتابا فى حياتى. |

إذا كانت العبارة الاولى تنطبق عليك فى الأسبوعين الأخيرين بما فى ذلك اليوم فضع علامة ( √ ) فى المربع المجاور لها تماما ، كما رأيت فى المثال السابق.

تذكر أنك تختار العبارة التى تصف مشاعرك وأفكارك فى الأسبوعين الأخيرين:

| | | |
|---|---|---|
| ١ | | إنى أشعر بالحزن أحيانا. |
| | | إنى أشعر بالحزن فى أوقات كثيرة. |
| | | إنى أشعر بالحزن طوال الوقت. |
| ٢ | | كل مايخصنى لايسير سيرا حسنا. |
| | | لست متاكدا من أن الأشياء والظروف سوف تسير سيرا حسنا. |
| | | الأشياء والظروف سوف تسير سيرا حسنا بالنسبة لى. |
| ٣ | | أنا أعمل أغلب الأشياء بطريقة جيدة. |
| | | أعمل أشياء كثيرة بطريقة خطأ. |
| | | أنا أعمل كل شىء بطريقة خطأ. |
| ٤ | | توجد أشياء كثيرة تسلينى. |
| | | بعض الأشياء والحاجات تسلينى. |
| | | لايوجد شىء يسلينى. |

٥
- [ ] فى كل الأوقات أنا سيىء.
- [ ] فى أوقات كثيرة أكون سيئا.
- [ ] أحيانا أكون سيئا.

٦
- [ ] أحيانا أفكر فى أشياء سيئة (غير مستحبة) تحدث لى.
- [ ] أنا قلق ومشغول من بعض الأشياء السيئة أو غير المستحبه التى تحدث لى.
- [ ] أنا متاكد من أشياء سيئة أو غير مستحبة تحدث لى.

٧
- [ ] أنا أكره نفسى.
- [ ] أنا لا أحب نفسى.
- [ ] أنا أحب نفسى.

٨
- [ ] كل الأشياء السيئة أو غير المستحبه تحدث بسببى أنا.
- [ ] كثير من الأشياء السيئة أو غير المستحبه تحدث بسببى أنا.
- [ ] لا تحدث الأشياء السيئة أو غير المستحبه دائما بسببى أنا.

٩
- [ ] أنا لا أفكر فى أن أقتل نفسى.
- [ ] أنا أفكر كثيرا فى قتل نفسى ولكنى لن أفعل ذلك.
- [ ] أنا أريد أن أقتل نفسى.

١٠
- [ ] يوميا أشعر بأنى أريد أن أبكى.
- [ ] فى أوقات كثيرة أشعر أنى أريد أن أبكى.
- [ ] أحيانا أشعر أنى أريد أن أبكى.

١١
- [ ] توجد أشياء تضايقنى دائما.
- [ ] توجد أشياء تضايقنى فى أوقات كثيرة.
- [ ] توجد أشياء تضايقنى أحيانا.

١٢
- [ ] أنا أحب أن اكون مع الناس.
- [ ] أنا لا أحب أن اكون مع الناس أوقات كثيرة.
- [ ] أنا لا أريد أن أكون مع الناس أبدا.

١٣
- [ ] أنا لا أستطيع أن أقرر أو أحدد رأيى فى الأشياء.
- [ ] من الصعب على أن أقرر أو احدد رأيى فى الأشياء.
- [ ] أنا أقرر أو أحدد رأيى فى الأشياء بسهولة.

١٤
- [ ] أنا شكلى حسن.
- [ ] يوجد بعض الأشياء فى شكلى غير حسنه.
- [ ] أنا شكلى غير حسن.

١٥ يجب على أن أدفع نفسى طوال الوقت حتى أكمل واجبات المدرسة.
يجب على أن أدفع نفسى أكثر من مرة حتى أكمل واجبات المدرسة.
واجبات المدرسة ليست مشكلة كبيرة بالنسبة لى.

١٦ كل ليلة يصعب على النوم.
فى ليالى كثيرة يصعب على النوم.
أنا أنام جيدا.

١٧ أشعر أحيانا أنى مجهد أو متعب.
أشعر فى أوقات كثيرة بالإجهاد أو التعب.
أشعر طوال الوقت بالاجهاد أو التعب.

١٨ فى أغلب الايام لاتكون لدى شهية للطعام.
فى ايام كثيرة لاتكون لدى شهية للطعام.
أنا أكل بطريقة جيدة.

١٩ أنا غير قلق من أى الأم أو أوجاع.
فى مرات كثيرة أكون قلقا من بعض الآلام والاوجاع.
طوال الوقت اكون قلقا من الآلام أو الأوجاع.

٢٠ أنا لا أشعر بالوحدة.
فى أوقات كثيرة أشعر بالوحدة.
طوال الوقت أشعر بالوحدة.

٢١ لم أشعر بالمتعة فى المدرسة أبدا.
أحيانا أشعر بالمتعة فى المدرسة.
فى أوقات كثيرة أشعر بالمتعة فى المدرسة.

٢٢ لدى أصدقاء كثيرون.
لدى بعض الأصدقاء ، ولكن أتمنى أن يكون لدى أصدقاء اكثر.
أنا ليس لدى صديق واحد.

٢٣ عملى - شغلى - المدرسى جيد.
عملى المدرسى ليس جيدا كما كان من قبل.
عملى المدرسى سيىء جدا فى مواد كنت دائما جيدا فيها.

٢٤ أنا لايمكن أن أكون جيدا مثل بقية زملائى.
لو أردت فإنى أستطيع أن أكون جيدا مثل بقية زملائى.
أنا جيدا مثل بقية زملائى.

٢٥ | | في الحقيقة انه لا احد يحبنى.
| | أنا لست متاكدا من أن أحدا يحبنى.
| | أنا متاكدا من أن بعض الأشخاص يحبوننى.

٢٦ | | أنا عادة أعمل مايطلب منى.
| | فى أغلب الأوقات أنا لا أعمل مايطلب منى.
| | طوال عمرى لم أعمل مايطلب منى.

٢٧ | | أنا أنسجم مع الناس.
| | فى أوقات كثيرة أجد نفسى متورطا فى مشاجرات.
| | طوال الوقت أنا أتورط فى مشاجرات.

المجموع

| | |
|---|---|
| | |
| فردى | جماعى |

التطبيق

وشكرا لك على حسن تعاونك،

# *Arabic Summary*

# الملخص العربى

يعتبر الاكتئاب عرضاً مصاحبًا لأمراض أخرى ومعجزاً وهو يصيب حوالى ٢ إلى ٧% من الأطفال و٣ على ١٠% من المراهقين .

اثبت بعض الباحثين ان الإكتئاب يكون مرتبطا بثبيط المناعة خارج الجسم (معمليا) كما هو ثابت بالإختبارات الليمفاوية المتحوله، وبنقص عدد الخلايات "ت" و " ب" و بنقص الخلايا ذات النشاط الفتاك الطبيعى .

فى حين أن نتائج بعض الدراسات الأخرى تشير إلى وجود نشاط فى الخلايا الليمفاوية " ت " مصاحب لإضطراب الإكتئاب والتى تتميز بوجود زيادة فى الخلايا الليمفاوية "ت" النشطة والخلايا الليمفاوية "ت" الحاملة لمستقبلات الإنترلوكن -٢ و HLADR وزيادة نسبة مستقبلات الإنترلوكن - ٢ فى المصل .

والهدف من البحث هو دراسة الأعراض الأكثر شيوعاً فى مجموعات الإكتئاب المختلفة (المعتدل ، المتوسط والشديد) وأهم الأسباب المؤدية إلى الإكتئاب.

كما يهدف هذا البحث على دراسة مستقبل إنترلوكن -٢ لدى الأطفال المكتئبين وعلاقته بإختلاف شدة الإكتئاب .

وتتكون عينة البحث من ٦٠ مريض مصرى يتراوح أعمارهم من ٧ إلى ١٨ سنة ممن يعانون من إكتئاب ، وقد تم إختبار العينة من مركز الطب النفسى ، بكلية الطب بجامعة عين شمس .

وقد تم تقسيم الحالات إلى ٣ مجموعات تبعا لشدة الإكتئاب إلى بسيط ، متوسط وشديد الإكتئاب .

تم تطبيق الأتى على الحالات و المجموعة الضابطة :

- مقابلة طب نفسية (لإختيار الحالات والمجموعة الضابطة) .
- فحص عضوى شامل (لتجنب أى أمراض عضوية أخرى).

- أختبار الأكتئاب للأطفال (عبد الفتاح ١٩٩٣ ) وذلك ليمكننا ملاحظة الأعراض الغير واضحة – لدى الأطفال المكتئبين وليكون لدينا أرقام لكل عرض حتى يتثنى لنا عمل علاقات بينها وبين مستقبل الانترلوكن –٢
- وقد طبق المقياس المعدل للمستوى الإجتماعى الإقتصادى للأسرة المصرية الشخص (١٩٩٥) وقد وجد أن المستوى الإجتماعى الإقتصادى لأسر العينة يقع ما بين المتوسط وفوق المتوسط .
- وقد تم تشخيص الحالات وتقسيمها إلى معتدل ، متوسط وشديد الأكتئاب وبإستخدام التصنيف الدولى العاشر لمرض الإكتئاب (١٩٩٢) بواسطة الباحث .
- وأخيرا تم قياس مستقبلات الإنترلوكن –٢ فى المصل بطريقة الإليزا.
- وقد طبقت التحاليل الإحصائية مستخدما (المتوسط ، الإنحراف المعيارى – اختبارات، إختبار كا$^{٢}$ ' أنوفا ، معامل الإرتباط .

وقد نوقش النتائج فى ضوء ما توفر من مراجع فى هذا الصدد وقد وجد أن إنتشار الإكتئاب لدى الفتيات أكثر منه عند الذكور (٦٣,٣% فتاة : ٣٦,٧ % فتى ) .وذلك يتماشا مع أراء العديد من الباحثين بينما يختلف عن أخرين وذلك الاختلاف يرجع إلى أن معظم عينة هذا البحث كانت من المراهقين (٤٦ حالة) ، بينما الاطفال ١٤ حالة فقط .

وقد وجد أن الأعراض الأتية وهى : الحزن ، فقدان القدرة على الإستمتاع ، والإجهاد منتشرة بنسبة ١٠٠% وذلك لان التصنيف الدوري العاشر لمرض الأكتئاب (١٩٩٢) المستخدم فى تشخيص وتقسيم الحالات يعتبر هذه الأعراض من الأعراض الأساسية فى التشخيص فى كل المرضى بالإكتئاب فى هذه العينة وهناك أعراض أخرى منتشرة بنسبة ١٠٠% فى مجموعة الإكتئاب الشديد وهى : التشاؤم ، الشعور بالفشل ، وفقدان الشهية للطعام كما نجد التفكير فى الأنتحار والشعور بالذنب بنسبة ٩٠% كما نجد الأعراض العضوية والشعور بالوحدة والعزلة الإجتماعية جميعهم بنسبة ٨٠% وكذلك نجد مجموعة الإكتئاب المتوسط الشدة ينتشر

فيها التفكير فى الإنتحار والشعور بالعزلة بنسبة ١٠٠% كما نجد العزلة الإجتماعية بنسبة ٩٠% والأعراض العضوية والتشاؤم بنسبة ٨٠ % .

ولقد وجد أن عدم الإستمتاع بالدراسة وتدهور التحصيل الدراسى بنسبة ٨٠ % فى مجموعة الإكتئاب الشديد . وقد وجد أن هناك فارق ذو دلالة إحصائية بين مجموعة الإكتئاب الشديد والمجموعة الضابطة فى الإعراض السابقة بينما لا يوجد فرق ذو دلالة إحصائية لدى عرض نقص الحافز الدراسى ( على الرغم من أن نسبته قد بلغت ٨٠% فى مجموعة الإكتئاب الشديد و ٧٠ % لدي مجموعة الأكتئاب المتوسط وذلك يرجع إلى ثقل الواجبات المدرسية والمناهج الدراسية مما جعل الأصحاء أيضا يبغضونها .

وقد وجد أن هناك فارق ذا دلالة إحصائية بين فقدان أحد أوكلا الوالدين فى الحالات والمجموعة الضابطة وقد تمشي هذا الري مع العديد من الباحثين بينما أختلف مع باحثين من الدول الغربية ويرجع هذا التباين فى وجهات النظر إلى ترابط الأسر المصرية والعلاقات الحميمة بينها بينما نجد التفكك الأسري والطباع المختلفة التي تميل إلى أستقلال الأبناء فى الخارج مما يجعل وجود أوليا الأمور من عدمه شيئا غير مؤثر وقد وجد إيضا أن هناك فارقا ذا دلالة إحصائية بين مرض الأم بالإكتئاب فى الحالات والأصحاء وذلك بسبب إما عوامل جينية وراثية أو عوامل بيئية أو كليهما معا .

وقد وجد أن مستوى مذاب مستقبل أنترلوكن –٢ فى المصل قد إزداد إزديلداً ذا دلالة إحصائية فى مرضى الإكتئاب عنه فى الأصحاء . وأيضا عند مقارنة الإكتئاب الشديد والمتوسط الشدة بالإكتئاب معتدل الشدة أو بالمجموعة الضابطة فإننا نجد فرق ذا دلالة إحصائية. بينما إذا قارنا الإكتئاب المتوسط بالإكتئاب الشديد أو إذا قارنا المجموعة الضابطة بمجموعة الإكتئاب المعتدل فإننا لا نجد فروقا ذات دلالة إحصائية وذلك يرجع إلى نشاط الخلية ت واكتسابها إنترلوكن ٢ بداية من مرحلة الإكتئاب المتوسط .

هذا وقد إظهرت علاقة مذاب مستقبل إنترلوكن -٢ بالجنس أن هناك ايضا فرق ذا دلالة إحصائية فى حالة مجموعة الإكتئاب الشديد فقط وأن المتوسط الحسابى أعلى فى الذكور عنه فى الإناث فى هذه المجموعة ( مع العلم بأنه لا يوجد فرق ذو دلالة إحصائية بين أى جنس فى المجموعة الضابطة ) وذلك قد يرجع إلى تأثر مستقبل إنترلوكن ٢ بالتدخين وبممارسة الرياضة وكليهما يتوفر أكثر فى الذكور عنه فى الأناث .

كما أظهرت علاقة مستوى مذاب مستقبل إنترلوكن -٢ فى حالة مجموعة الإكتئاب الشديد المصاحبة بإكتئاب لدى الإمهات وبين نفس المجموعة التى ليس عند إمهاتهم مرض نفسى فرق ذو دلالة إحصائية .

كذلك أظهرت علاقة مستوى مذاب مستقبل إنترلوكن -٢ بين مرضى الإكتئاب الذين يعانون من إضطرابات فى النوم وبين مرضى الإكتئاب الخالين من الإضطرابات النومية فرقا ذا دلالة إحصائية.

وأخيراً لقد وجد أن ليس هناك إرتباط بين مستوى مستقبل إنترلوكن -٢ والآتى : الحالة الإجتماعية الإقتصادية للأسرة ، وسن الطفل ، وعدد أولياء الأمور المقيمين مع الطفل ، ومرض الأم النفسى فرق ذا دلالة إحصائية.

وقد توصل البحث إلى النتائج الآتية:

١. أن الإكتئاب يكون أكثر لدي الإناث عنه لدي الذكور .

٢. أن الحزن ، وفقدان الاستمتاع والأجهاد أعراض منتشرة جداً لدي جميع مرضي الإكتئاب.

٣. وأن التحصيل الدراسي والإستمتاع بالمدرسة توجد بنسبة ٨٠ % لدي مجموعة الإكتئاب الشديد ، مع وجود فارق ذا دلالة إحصائية بين مجموعة الإكتئاب الشديد والمجموعة الضابطة.

٤. كما أن فقدان احد أو كلا الوالدين يمكن أن يزيد القابلية للإصابة بمرض الإكتئاب .

٥.كما وجد أيضا أن مستوي مذاب مستقبل إنترلوكن- ٢ فى المصل يزيد فى حالات الإكتئاب عنه لدي الأصحاء وهذه الزيادة لها علاقة طردية مع زيادة شدة المرض .

٦. أيضا وجد أن مستوي مذاب مستقبل إنترلوكن -٢ فى المصل يزيد لدي الذكور المصابين بإكتئاب حاد .

٧.كما أن مرض الام النفسي يؤثر على مستوي مستقبل إنترلوكن -٢ فى المصل فى حالات الإكتئاب الشديد فقط .

٨.وأخيرا وجد أن إضطراب النوم الشديد لديه تأثير شديد على مستوي مستقبل إنترلوكن - ٢.

وبناء عليه يوصي البحث بالأتى :

١. أن يحدد مدي قيمة المستوي الطبيعى لمستقبل إنترلوكن-٢ فى المصل والتى يمكننا الرجوع إليها.

٢. إن علاج مرضي الإكتئاب فى وقت مبكر لدي المصابين بإضطراب مناعى يؤدي إلى تحسين عواقب المرض .

٣.كما يوصي البحث بإستخدام مذاب مستقبل إنترلوكن -٢ كواحد من دلائل شدة الإكتئاب (المتوسط أو الشديد).

٤.فى النهاية يوصي البحث بإجراء أبحاث أخري للتعرف على سبب زيادة مذاب مستقبل إنترلوكن - ٢ فى الذكور المصابين بإكتئاب شديد عنه فى الإناث .

# مستخلص الرسالة


**الاسم** : وفاء مصطفى محمد الجنيدي


**عنوان الرسالة** : مستقبل إنترلوكن – ٢ فى إكتئاب الأطفال


**جهة البحث** : معهد الدراسات العليا للطفولة



**المستخلص** : فى هذا البحث تم إختيار عينة مكونة من ٦٠ طفل مصري يتراوح أعمارهم ما بين ٧ إلى ١٨ سنة من مركز الطب النفسي بجامعة عين شمس وتم تقسيم الحالات إلي ٣ مجموعات تبعا لشدة المرض.

وقد تم تطبيق الآتى على الحالات (وعددهم ٦٠ حالة) والمجموعة الضابطة (وعددهم ٢٠ طفلا):

مقابلة طب نفسية، فحص عضوي شامل ، إختبار الإكتئاب للأطفال ،المقايس المعدل للمستوي الإجتماعيى الإقتصادي للأسرة المصرية ، قياس مستقبل إنترلوكن –٢ فى المصل بطريقة الإيليزا .

وقد أثبتت نتائج هذا البحث الآتى :

إن عدد الإناث أكثر من عدد الذكور لدي مرضي الإكتئاب .

وقد وجد أن هناك فارقا ذا دلالة إحصائية بين فقدان احد أو كلا الوالدين فى الحالات والمجموعة الضابطة وأيضا بين مرض الأم بالإكتئاب فى الحالات والأصحاء .

كما وجد أن مستوي مذاب إنترلوكن –٢ فى المصل قد إزداد إزديادا ذا دلالة إحصائية فى مرضي الإكتئاب عنه فى الأصحاء تبعا لشدة المرض .

كما أظهرت علاقة مذاب مستقبل إنترلوكن –٢ بالجنس فرق ذا دلالة إحصائية فى حالة مجموعة الإكتئاب الشديد فقط وأن المتوسط الحسابي أعلي فى الذكور عنه فى الإناث .

كما أظهرت علاقة مستوي مذاب مستقبل إنترلوكن –٢ لدي مجموعة الإكتئاب الشديد المصاحب بإكتئاب لدي الأمهات وبين نفس المجموعة التي ليس عند أمهاتهم مرض نفسي فرقا ذا دلالة إحصائية.

وأخيرا أظهرت علاقة مستوي مذاب مستقبل إنترلوكن–٢ بين مرضي الإكتئاب الذين يعانون من إضطرابات نومية وبين مرضي الإكتئاب الخالين من الإضطرابات النومية فرقا ذا دلالة إحصائية.



**الكلمات المفتاحية :**

الأكتئاب – إكتئاب الأطفال – إنترلوكن –٢– مستقبل إنترلوكن –٢ – مذاب مستقبل إنترلوكن –٢– المناعة لدي المصابين بالإكتئاب .

جامعة عين شمس
الكلية : معهد الدراسات العليا للطفولة
قسم الدراسات الطبية

# شكـــــــر

اشكر السادة الأساتذة الذين قاموا بالأشراف وهم

١- أ.د/ عادل جمال المسيري

٢- أ.د/ نجلاء ناجي المحلاوي

٣- أ.د/ علوية محمد عبد الباقي

٤- أ.د.م/ راندة عبد الوهاب رضا مبروك

ثم الأشخاص الذين تعاونوا معي في البحث وهم

١- أ.د/ عفاف حامد خليل

٢- د./ نهلة السيد ناجي

٣- د./ مديحه احمد عمر

وكذلك الهيئات الاتية :

١- مركز الطب النفسي - جامعة عين شمس

جامعة عين شمس .

الكلية : معهد الدراسات العليا للطفولة .

قسم : الدراسات الطبية .

صفحة العنوان

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| اسم الطالبة | : | وفاء مصطفى محمد الجنيدي |
| الدرجة العلمية | : | دكتوراه فى دراسات الطفولة |
| القسم التابع له | : | قسم الدراسات الطبية |
| اسم الكلية | : | معهد الدراسات العليا للطفولة |
| الجامعة | : | عين شمس |
| سنة التخرج | : | ٢٠٠١ |
| سنة المنح | : | ٢٠٠١ |

**جامعة عين شمس**
**الكلية : معهد الدراسات العليا للطفولة**
**قسم الدراسات الطبية**

رسالة دكتوراة
**اسم الطالبة : وفاء مصطفي محمد الجنيدي**
عنوان الرسالة : مستقبل انتر لوكن ٢ في اكتئاب الاطفال

اسم الدرجة : دكتوراة
**لجنة الاشراف :**

| | |
|---|---|
| ١- الاسم/ أ.د **عادل جمال المسيري** | الوظيفة/ استاذ ورئيس مركز البحوث الطبية بجامعة عين شمس |
| ٢- الاسم/ أ.د **نجلاء ناجي المحلاوي** | الوظيفة/ استاذ طب نفسي بجامعة عين شمس |
| ٣- الاسم/ أ.د **علوية محمد عبد الباقي** | الوظيفة/ استاذ بقسم الدراسات الطبية – معهد الدراسات العليا للطفولة بجامعة عين شمس |
| ٤- الاسم/ أ.م.د **راندة عبد الوهاب رضا مبروك** | الوظيفة/ استاذ مساعد كلينيكال باثولوجي بكلية الطب جامعة عين شمس |

تاريخ البحث : ٢٠ / ٢ /١٩٩٥

**الدراسات العليا**
**ختم الاجازة :** اجيزت الرسالة بتاريخ /٨/٨/ ٢٠٠١

**موافقة مجلس الكلية**
١٧ / ٤ /٢٠٠١

**موافقة مجلس الجامعة**
/ /٢٠٠١


بسم الله الرحمن الرحيم


# مستقبل إنترلوكن - ٢
# في إكتئاب الأطفال

رسالة عملية
للحصول على درجة دكتوراه الفلسفه

في
دراسات الطفولة الطبية



مقدمه من
الطبيبة / وفاء مصطفى البنداري

بكالوريوس الطب والجراحة ، ماجستير دراسات طفولة

وماجستير طب أطفال جامعة عين شمس

تحت إشراف

أ.د. عادل المسيري
أستاذ ورئيس مركز
البحوث الطبية
جامعة عين شمس

أ.د. نجلاء المحلاوى
أستاذ الطب النفسى
جامعة عين شمس

أ.د. علوية عبد الباقى
أستاذ طب نفسى أطفال
معهد دراسات الطفولة
جامعة عين شمس

أ.م.د. رائدة عبد الوهاب
رضا مبروك
أستاذ مساعد الباثولوجى الإكلينيكيه
جامعة عين شمس

جامعة عين شمس
معهد الدراسات العليا للطفولة
قسم الدراسات الطبيه
٢٠٠١