بسم الله الرحمن الرحيم

Sudan University for Science and Technology

College of Graduate Studies

Assessment of Complete Blood Count and Iron Profile Among Sudanese Patients with Depressive Disorders

تقييم تعداد الدم الكامل ومستوى الحديد بين المرضى السودانيين الذين يعانون من الإضطرابات الإكتئابية

A dissertation submitted in partial fulfillment of the requirements for the M.Sc. Degree in Hematology and Immunohematology

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الآيـــة

بِسْـمِ اللّهِ الرَّحْمَنِ الرَّحِيـمِ

قال تعالى:

﴿ قَالُواْ سُبْحَانَكَ لاَ عِلْـمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيـمُ

الْحَكِـيـمُ ﴾

سورة البقرة الآية(32)

Dedication

To my parents…

To my sister and brothers…

To my friends …

Acknowledgement

First and foremost, we would like to thank God Almighty for giving us the strength, knowledge, ability and opportunity to undertake this research study and to persevere and complete it satisfactorily. Without his blessings, this achievement would not have been possible.

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Abstract

Depressive disorders, a group of illnesses characterize by Depression for a long period of time and Loss of interest in activities which causes serious physical and social dysfunction in individuals and severely disrupt the person's life.

This is a cross-sectional study intended to evaluate of complete blood count and iron profile among Sudanese patients with depressive disorders in Omdurman, Sudan. Short questionnaire was administered on the randomly chosen, and fifty blood samples were collected and performed complete blood count (CBC), blood film and iron profile for each participant. The data was entered and analyzed by SPSS program (version 16) and compared with international studies. The Result showed that CBC parameters were normal comparing with reference value as follows: RBCs (Mean = 4.75vs. 4.2-6.1$\times10^{12}$/L), Hb (Mean = 13.2vs. 12-18 g/dl), HCT (Mean = 42.44vs. 37-54 %), MCV(Mean = 89.33vs. 80-96 fl), MCH(Mean =27.73vs. 27-32 pg.) , MCHC(Mean = 31.11vs. 32-36 g/dl), platelets count (Mean = 227.64 vs. 145-400 $\times10^{9}$/L), TWBCs (Mean =5.5 vs. 4.0-10.0 $\times10^{9}$/L), Serum iron (Mean = 16.47 vs. 7.16-31.3 mmol/L), Ferritin (Mean = 89.97 vs. 20-250 µg/L), TIBC (Mean = 60.02 vs. 36-72 µmol/L), Transferrin Saturation (Mean = 27.96 vs. 20-50 %). The association between severity of depression and low Hb level is significant (P. Value= 0.007). The association between severity of depression and iron deficiency anemia was insignificant (P. Value= 0.951).

We concluded that normal complete blood count and iron profile noted in majority of depressed patient with statistical significant in all hematological parameters except MCV, Mix, and TIBC which statistical insignificant in depressed patients when compared with mean of reference values, and there is a relation between low hemoglobin level and depressive disorders while there is no

relation between iron deficiency anemia, socio-demographic factors with severity of depressive disorders.

ملخص الدراسة

الاضطرابات الاكتئابية ، وهي مجموعة من الأمراض التي تتميز بالاكتئاب لفترة طويلة من الزمن وفقدان الاهتمام في الأنشطة التي تسبب اختلال وظيفي جسدي واجتماعي خطير في الأفراد وتعطيل حياة الشخص بشدة. هذه دراسة مستعرضة تهدف إلى تقييم تعداد الدم الكامل والحديد بين المرضى السودانيين الذين يعانون من اضطرابات الاكتئاب في أم درمان، السودان. تم إعطاء استبيان قصير على اختيار عشوائي. و تم جمع خمسين عينة دم وأجرى اختبار خلايا دم كاملة (CBC) و فيلم دم و اختبار الحديد لكل مشارك. تم إدخال البيانات وتحليلها من قبل برنامج الإحصاء (SPSS) الإصدار (16) ومقارنتها مع الدراسات الدولية. وتبين النتائج أن معاملات CBC كانت كما يلي:

كرات الدم الحمراء ($Mean = 4.75vs. 4.2-6.1\times10^{12}/L$), والهيموقلوبين ($Mean = 13.2vs.$ 12-18 g/dl) و خضاب الدم ($Mean = 42.44vs.$ 37-54 %), و حجم خلية الدم ($Mean =$ 89.33vs. 80-96 fl), و معدل تركيز خضاب الدم الكروي ($Mean =27.73vs.$ 27-32 pg) و معدل تركيز خضاب الدم في الخلية ($Mean = 31.11vs.$ 32-36 g/dl) و عدد الصفائح الدموية ($Mean = 227.64$ vs. 145-400 $\times10^{9}/L$) و كريات الدم البيضاء ($Mean =5.5$ vs. 4.0-10.0 $\times10^{9}/L$) و Serum iron ($Mean = 16.47$ vs 7.16-31.3mmol/L) و Ferritin ($Mean =$ 89.97 vs 20-250 µmol/L) و TIBC ($Mean =60.02$ vs 36-72 µmol/L) و Transferrin Saturation ($Mean = 27.96$ vs. 20-50 %) العلاقة بين شدة الاكتئاب وانخفاض مستوى الهيموقلوبين كبيرة (P value =0.007), بينما العلاقة بين شدة الاكتئاب وفقر الدم بسبب نقص الحديد غير ذات أهمية (P value =0.951).

استنتج من الدراسه أن تعداد الدم الكامل والحديد طبيعي في غالبية المرضى الذين يعانون من الاكتئاب، مع وجود فروقات ذات دلالة إحصائية معنويه في جميع المعلمات الدموية باستثناء MCV و Mix و TIBC

والتي ليست فروقات ذات دلالة إحصائية معنويه في مرضى الاكتئاب عند مقارنتها بمتوسط القيم المرجعية.

ولاحظ أن هناك علاقة بين انخفاض مستوى الهيموقلوبين واضطرابات الاكتئاب في حين لا توجد علاقة بين فقر الدم بسبب نقص الحديد ، والعوامل الاجتماعية والديموغرافية مع شدة اضطرابات الاكتئاب.

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List of abbreviations

Abbreviations	Full Text
4MUP	4-methyl-umbelliferyl phosphate
AIA-PACK	Automated immunoassay analyzer package
BFU	Burst-forming unit
BFU-E	Burst-forming unit-erythroid
BFU-M	Burst-forming unit-macrophage
BMI	Body mass index
CASI C	Cognitive Abilities Screening Instrument Chinese version
CES-D	Epidemiologic Studies Depression scale
CBCs	Complete blood counts
CDR	Clinical Dementia Rating Scale
CFU-E	Colony-forming units-erythroid
CFU-GEMM	Colony-forming units-granulocytes-erythrocyte-macrophage-megakaryocyte
CFU-GM	Colony-forming units-granulocyte-macrophage
CFU-M	Colony-forming units-macrophage
CO2	Carbon dioxide
CRH	Corticotropin-releasing hormone
Dcytb	Duodenal cytochrome b
DD	Depressive Disorder
DMT1	Divalent metal transporter 1
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSS	Depressive symptom scores
ECT	Electroconvulsive therapy

EDTA	Ethylene diamine tetra acetic acid
Fe+2	Ferrous
Fe+3	Ferric
GABA	Gamma amino butyric acid
GDS-15	Geriatric Depression Scale
HAM-D	Hamilton Depression Rating Scale
Hct	Hematocrit
HDRS	Hamilton depression rating scale
HDW	Haemoglobin distribution width
HGB	Hemoglobin
HPA	Hypothalamus, pituitary, and adrenal glands
HSCs	Hematopoietic stem cells
ID	Iron deficiency
IDA	Iron deficiency anemia
IgE	Immunoglobulin E
IREG-1	Iron-regulated transporter 1
LED	Light emitting diode
MCH	Mean corpuscular hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean corpuscular volume
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
MPV	Mean platelet volume
MRI	Magnetic resonance imaging
MTP1	Metal tolerance protein 1
PBP	Peripheral blood picture
PCV	Packed cell volume

PLT	Platelet
PPD	Post-partum depression
RBCs	Red blood cells
RDW	Red cell distribution width
Rtms	Repetitive transcranial magnetic stimulation
SDA	Seasonal affective disorder
SDS	Self-rating Depression Scale
SERT	Serotonin transporter
SI	Serum iron
SPSS	Statistical package for social science
SSRIs	Selective serotonin reuptake inhibitors
ST AIA-PACK FER package ferritin	Stat Automated immunoassay analyzer
TCLSI Health	Tianjin Chronic Low-grade Systemic Inflammation and Health
TIBC	Total iron binding capacity
UIBC	Unbound iron binding capacity
WBCs	White blood cells
WHO	World Health Organization

Chapter one

Introduction and Literature review

1.1 Introduction

Iron deficiency anemia (IDA) arises when the balance of iron intake, iron stores, and the body's loss of iron are insufficient to fully support production of erythrocytes (Miller, Schaer and Buehler, 2013). According to the World Health Organization, iron deficiency (ID) is the most prevalent nutritional deficiency(Chen *et al.*, 2013). It is the most important cause of a microcytic hypochromic anemia, in which the two red cell indices MCV (mean corpuscular volume) and MCH (mean corpuscular hemoglobin) are reduced and the blood film shows small (microcytic) and pale (hypochromic) red cells. This appearance is caused by a defect in hemoglobin synthesis (Hoffbrand, Moss and Pettit, 2006). An iron deficiency anemia does not develop rapidly in most cases (Turgeon, 2012). Its Results from three abnormalities affecting iron: loss from abnormal bleeding, deficient diet, and malabsorption (Stass, Schumacher and Rock, 2000).When the body is in a state of negative iron balance, the first event is depletion of body stores, which are mobilized for hemoglobin production. Iron absorption is increased when stores are reduced, before anemia develops and even when the serum iron level is still normal, although the serum ferritin will have already fallen (Hoffbrand, Catovsky and Tuddenham, 2005).With further iron depletion, when the serum ferritin is below 15 g/L, the serum transferrin saturation falls to less than 15% due to a rise in transferrin concentration and a fall in serum iron. This leads to the development of iron-deficient erythropoiesis and increasing concentrations of serum transferrin receptor and red cell protoporphyrin. At this stage, the hemoglobin, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) may still be within the reference range, although they may rise significantly when iron therapy is given. (Hoffbrand, Catovsky and Tuddenham, 2005)If the negative balance continues, frank iron deficiency anemia develops. The red cells become obviously

microcytic and hypochromic and poikilocytosis becomes more marked. The MCV and MCH are reduced, and target cells may be present. The reticulocyte count is low for the degree of anemia. The serum TIBC rises and the serum iron falls, so that the percentage saturation of the TIBC is usually less than 10% (Hoffbrand, Catovsky and Tuddenham, 2005). Infants with anemia showed slower psychomotor and mental development, and many of these effects seem irreversible (Lozoff *et al.*, 2000, 2006). Depressive Disorder (DD) is one of the most common mental disorders. Etiology of depressive disorder is classified into two major categories, i.e. non-modifiable (genetic) and modifiable (environmental). Nutrition is an important modifiable etiological factor. The clinical presentation of iron deficiency anemia patients often mimics that of depressive disorder. (Shafi *et al.*, 2018). New insights are emerging from recent and ongoing investigations into the role of iron in neurocognitive and neurobehavioral development. The uptake of iron through the blood–brain barrier appears to be regulated and dependent on iron status (Beard, 2003) such that there is a higher rate when iron status is low and a lower rate when it is high. (Beard, 2003)' (Taylor, Crowe and Morgan, 1991) .In addition, this uptake process is highly selective and not reflective of overall blood–brain barrier permeability. (Crowe and Morgan, 1992; Beard, 2003) .The brain obtains iron primarily via transferrin and transferrin receptors expressed in endothelial cells on the brain microvasculature. (Beard, 2003; Han *et al.*, 2003) .There appears to be a regulatory role for adjacent astrocytes in the regulation of this uptake across the blood–brain barrier. Iron deficiency affects neurogenesis and neurochemistry during brain development. (Rao *et al.*, 2003) .The role of iron in the production of hormones from the monoaminergic pathways, particularly dopamine and norepinephrine, illustrates the importance of iron in neurochemistry(Beard, 2003; Beard, Wiesinger and Connor, 2003; Burhans *et al.*, 2006). Iron deficiency

is also known to affect neurochemistry in the developing brain. Neurotransmitter metabolism and brain energy metabolism are affected negatively in iron deficiency, and iron replacement therapy is found to improve the mental development score. (Chen, Beard and Jones, 1995; Beard, Erikson and Jones, 2002; Sachdev, Gera and Nestel, 2005). Previous studies showed that iron deficiency anemia in children contributed to the development of anxiety, depression, social and attention-deficit disorders. (Lozoff *et al.*, 2000)Similarly, an association between low serum ferritin levels and depression has been reported even in the absence of iron deficiency anemia. (Shariatpanaahi *et al.*, 2007).

1.2 Literature Review

1.2.1 Definition of Psychiatric Disorders

A group of signs and symptoms characterized by clinically significant disturbance in an individual's cognition, mental illness that greatly disturbs your thinking, moods, emotion regulation , or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental function and seriously increases your risk of disability, pain, death, or loss of freedom.(Salters-pedneault, 2019).

Psychiatric disorders are diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Heugten-Van Der Kloet and van Heugten, 2015).

1.2.2 Types of Psychiatric Disorders

1-Neurodevelopmental Disorders

2-Schizophrenia Spectrum and Other Psychotic Disorders.

3-Bipolar and Related Disorders.

4-Depressive Disorders

5-Anxiety Disorders

6-Obsessive-Compulsive and Related Disorders

7-Trauma- and Stressor-Related Disorders.

8-Dissociative Disorders

9-Somatic Symptom and Related Disorders

10 - Feeding and Eating Disorders

11- Elimination Disorders.

12-Sleep-Wake Disorders.

13-Sexual Dysfunctions.

14-Gender Dysphoria.

15-Disruptive, Impulse-Control, and Conduct Disorders.

16-Substance-Related and Addictive Disorders.

17-Neurocognitive Disorders.

18-Personality Disorders.

19-Paraphilic Disorders.

20-Other Mental Disorders. (Talmage, 2018; Salters-pedneault, 2019).

1.2.3 Depressive Disorders

Depression is a word generally describes the feelings of sadness and unhappiness, when faced with stress such as great disappointment or frustrated, but these are emotional reactions associated with situation and will disappear in limited time. (Australian Government Department of Health and Ageing, 2014).

Depressive disorders are a group of illnesses characterize by Depression for a long period of time and Loss of interest in activities which causes serious physical and social dysfunction in individuals and severely disrupt the person's life. in this case the Professional assessment and treatment is necessary.(Australian Government Department of Health and Ageing, 2014; Körük and Özabacı, 2018).

1.2.3.1 Signs and Symptoms of Depressive Disorders

According to the DSM, 5+ of the following symptoms must be present for 2 weeks:

1. Depressed mood every day

2. A loss of interest in activities those normally are pleasurable including sex every day.

3.Appetite and Significant weight changes (either loss or gain)

4.Sleep disturbances (insomnia, hypersomnia early morning wakening, or oversleeping) every day.

5. Feelings of guilt, worthlessness, or helplessness.

6. Feelings of hopelessness or pessimism.

7. Difficulty in concentrating, remembering, or making decisions

8. Thoughts of death or suicide; suicide attempts.

9. Persistent body aches and pains or digestive disorders not caused by physical disease.

10. Psychomotor agitation or retardation every day.

11. Fatigue every day.

Anyone who experiences five or more of these symptoms for at least 2 weeks may have a depressive illness and should seek the advice and assistance of a psychiatrist or other doctor. (American Psychiatric Association, 2000).

1.2.3.2 Severity of Depressive Disorders

Mild at least 2 main symptoms, plus at least 2 accessory symptoms, none of the symptoms intense.

Moderate at least 2 main symptoms, plus at least 3 accessory symptoms; some symptoms marked.

Severe all 3 main symptoms, plus at least 4 accessory symptoms; some symptoms severe with intensity (Baghai, Eser and Möller, 2008).

1.2.3.3 Causes of Depressive Disorders

According to the U.S. Department of Health and Human Services (1999), the exact causes of depressive disorders are not known there is evidence.

1.2.3.3.1 Genetic factors

Specific genes passed from one generation to the next contributes to a child's vulnerability to a depressive(Virginia Commission on Youth, 2017) . There is strong evidence that genetic factors play a significant role in a person's predisposition towards developing depression, especially melancholic depression, psychotic depression and bipolar disorder. The genetic risk of developing clinical depression is about 40% if a biological parent has been diagnosed with the

illness, with the remaining 60% being due to factors within the individual's own environment (Leffingwell, 1931).

Researchers now realize that inherited factors are important. In other words, having close relatives who have had depression means that you are more likely to become depressed. People with a genetic susceptibility may be more vulnerable to depression when something upsetting happens(Lincoln *et al.*, 2010).

1.2.3.3.2 Biochemical factors

Depressive disorders are thought to be due, in part, to a chemical imbalance in the brain.(Australian Government Department of Health and Ageing, 2014).

Disturbances in brain biochemistry (the chemicals in the brain and how they work) are an important factor in depression. Irregularities in specific brain chemicals, called neurotransmitters, occur in depression(American Psychiatric Association, 2000).

Neurotransmitters are chemicals that carry signals from one part of the brain to the next. However, three important ones that affect a person's mood are serotonin, noradrenaline and dopamine.(Leffingwell, 1931)

Serotonin is responsible for regulating many of the body's functions such as mood, appetite, sleep, aggression, and sexual behavior. Norepinephrine is believed to aid in recognizing and responding to stressful situations. Dopamine regulates the drive to seek out rewards and pleasure (Nelson, 2012)

Brain imaging technologies, such as magnetic resonance imaging (MRI), have shown that the parts of the brain involved in mood, thinking, sleep, appetite, and behavior of people who have depression function differently than those of people without it (soterixmedical, 2019)

An emphasis upon physical and especially endocrine theories of causation has been encouraged by the observation that some physical illnesses increase the risk

of depression, including diabetes, cardiac disease, hyperthyroidism, hypothyroidism, Cushing's syndrome, Addison's disease and hyperprolactinaemic amenorrhea (Goldberg, 2006).

Serotonin hypothesis

It is a monoamine neurotransmitter with a wide distribution throughout the central nervous system.

Function: physiologic activities such as pain sensation, appetite regulation, aggression and mood.(Fekadu, Shibeshi and Engidawork, 2017).

1.2.3.3.3 Stress

Stress is perceived by the cortex of the brain and transmitted to the hypothalamus, where corticotropin-releasing hormone (CRH) is released onto pituitary receptors. This stimulus results in the secretion of corticotropin into plasma, stimulation of corticotropin receptors in the adrenal cortex, and release of cortisol into the blood. Hypothalamic cortisol receptors respond by decreasing CRH production to maintain homeostasis. The hypothalamic–pituitary–cortisol hypothesis of depression postulates that abnormalities in the cortisol response to stress may underlie depression. figure (1-1) (Belmaker and Agam, 2008). the normal cortisol-suppression response is absent in about half of the most severely depressed patients.(Penninx *et al.*, 2013).

Gamma amino butyric acid (GABA) is a naturally occurring amino acid act as a neurotransmitter in the brain. It is considered an inhibitory neurotransmitter because it inhibits certain brain signals and decreases activity of the nervous system. When Gamma amino butyric acid attaches to a protein in your brain known as a Gamma amino butyric acid receptor, it produces a calming effect. This can help with feelings of anxiety, stress, and fear. (Healthline, 2019).

It was reported that depression was accompanied by lower levels of GABA in cerebrospinal fluid (Anisman, Merali and Poulte, 2012).

The cortisol and its central releasing factor, Corticotropin-releasing hormone (CRH) and Gamma amino butyric acid (GABA) have been implicated in depression (Merali *et al*., 2004).

Chronic stress and hyperactivity of the HPA axis (causing chronic hypercortisolemia) have been hypothesized to play a prominent role in the incidence of depression and even in recurrence after complete remission. (Fekadu, Shibeshi and Engidawork, 2017).

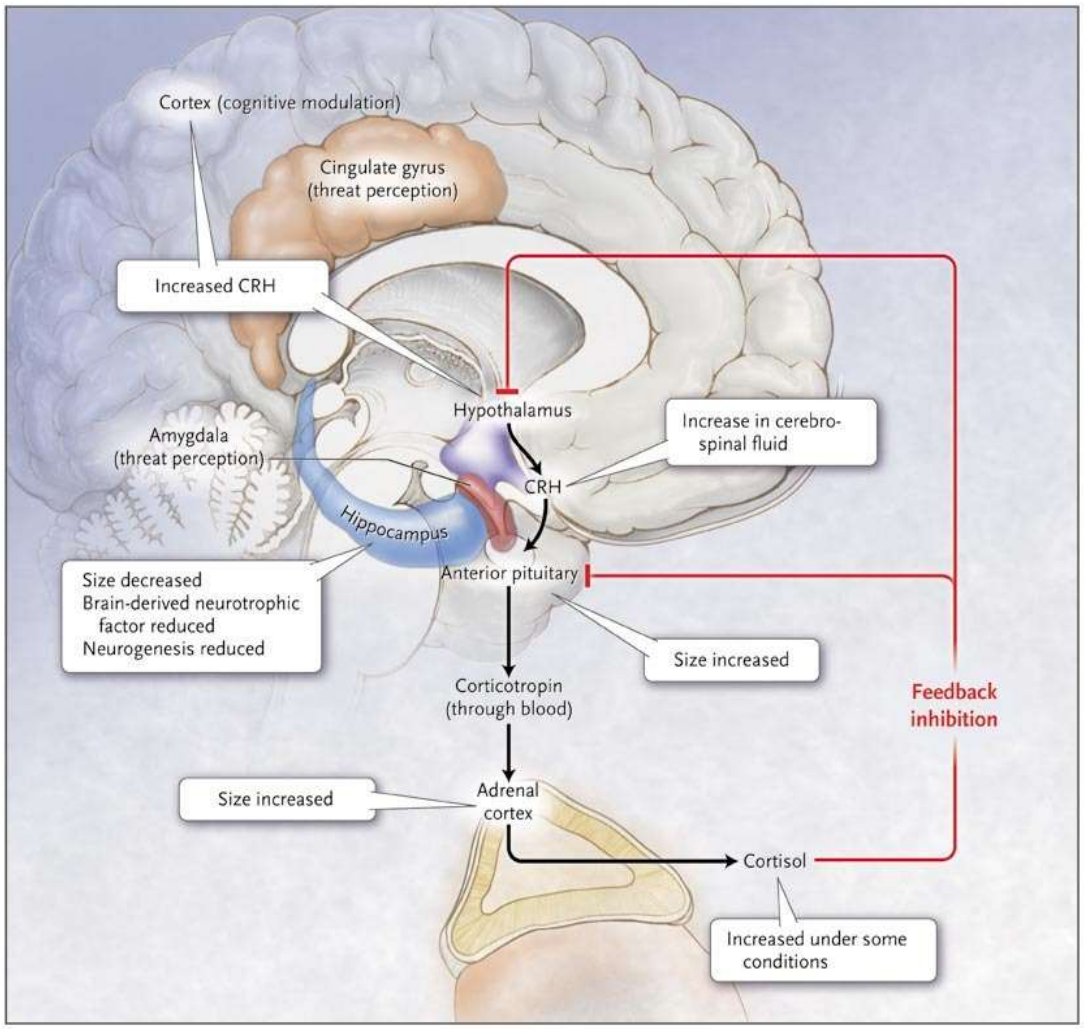


Figure (1-1): Hypothalamic-Pituitary-Cortisol System in Depression (Belmaker and Agam, 2008).

1.2.3.3.4 Temperament

People with certain temperaments are more prone to depressive symptoms. Depression commonly occurs in people who are highly anxious, sensitive, emotional, and react strongly to and are easily upset by events in their lives. People who are perfectionists and self-critical, and who set high standards for themselves and others, are vulnerable to depression. Those who are very dependent on other people are also susceptible to depression if they are let down.(Australian Government Department of Health and Ageing, 2014)

1.2.3.3.5 Alcohol and Other Drugs

Harmful alcohol and other drug use make people highly susceptible to depression.

This also contributes to a high risk of suicide for people with depressive disorders.(Australian Government Department of Health and Ageing, 2014)

1.2.3.4 Types of Depressive Disorders

There are diverse forms of depression that can either be mild or extremely severe (Fekadu, Shibeshi and Engidawork, 2017) .

The following are descriptions of categories of depressive disorders:

1.2.3.4.1 Major Depressive Disorder

Major depressive disorder, or as it is often called, "major depression," is a medical illness that affects how you feel, think and behave causing persistent feelings of sadness and loss of interest in previously enjoyed activates.(American Psychiatric Association , 2013).

1.2.3.4.1.1 DSM-IV Criteria for Major Depressive Disorder (MDD)

Onset of a Major Depressive Episode can be anywhere from days to a few weeks. Symptoms must be present for most of the day, nearly every day, for at least 2-weeks (Nelson, 2012).

Specific symptoms, at least 5 of these 9, present nearly every day:

1. Depressed mood (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. Decreased interest or pleasure
3. Significant weight change (5%) or change in appetite
4. Insomnia or hypersomnia
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Guilt/worthlessness
8. Diminished ability to think or concentrate, or more indecisiveness
9. Suicidality. (Pużyński, 2002)

1.2.3.4.1.2 Etiology of Major Depressive Disorder

There is no definitive cause of MDD has been identified. There are multiple theories that have been studied, summarized in the following:

Neurotransmitters, Structural changes, Inflammation and Genetics (Pużyński, 2002).

1.2.3.4.2 Dysthymic disorder

It is also known as Persistent Depressive Disorder (Virginia Commission on Youth, 2017) . The etymological meaning of dysthymia is "ill tempered" referring to a temper that tends towards Melancholy(Lima, 2004). the depressive symptoms are chronic and longer-term but symptoms are less severe than in major depressive disorder (Ministry of Health Singapore, 2004). Patients display depressed mood or sadness that persists for two years in adults and one year in children and adolescents (Fekadu, Shibeshi and Engidawork, 2017). Sometimes people with dysthymia also experience major depressive episodes, also called double depression (Lincoln *et al.*, 2010) If a person has had dysthymia for two

years and then has an episode of major depression in addition to the underlying dysthymic disorder, “double depression” is diagnosed (Setälä, 2002) . It involves the same symptoms of major depression disorders; sad mood accompanied with two or more of the following: low energy, poor appetite or overeating, and insomnia or oversleeping. It can show up as stress, irritability, and mild anhedonia, which is the inability to derive pleasure from most activities (adaa, 2019).

1.2.3.4.2.1 Subtypes of dysthymia

1.2.3.4.2.1.1 Early onset dysthymia

(Onset before the age of 21 years) associated with a higher risk of melancholia, more impairment, higher risk of recurrence of major depressive episodes and a higher risk of substance abuse in comparison to late-onset dysthymia. Risk factors include early trauma, family history, attention deficit hyperactivity disorder and incomplete recovery from major depression. (Trivedi and Kar, 2011).

1.2.3.4.2.1.2 Late Onset Dysthymia

(Onset at or after the age of 21 years). Risk factors include significant life stressors (e.g., death of a loved one/accident) and substance abuse (Trivedi and Kar, 2011).

1.2.3.4.2.1.3 Anergic Dysthymia

is characterized by a feeling of anergia (lack of energy), anhedonia, loss of libido, weight loss and excessive sleep.it is common in males and respond better to dopaminergic and noradrenergic agents (Trivedi and Kar, 2011).

1.2.3.4.2.1.4 Anxious dysthymia

is characterized by a feeling of subjective restlessness, sense of insecurity, impulsivity and low self-esteem.it is common in females and responds well to

serotonergic agents (selective serotonin reuptake inhibitors [SSRIs]) (Trivedi and Kar, 2011).

1.2.3.4.3 Melancholic Depression

Diagnostic criteria require lack of ability to experience pleasure. Psychomotor retardation and early morning worsening of mood is also apparent in this subset of patients. This type of depression is seen more commonly in the elderly, in patients with more severe forms of depression and psychotic depression.it has been reported that melancholic depression is more common in inpatients.(Benazzi, 2006).

1.2.3.4.4 Seasonal Affective Disorder (SAD)

It is depression that's related to certain seasons. It tends to happen during fall or winter. People with seasonal affective disorder have difficulty regulating the neurotransmitter serotonin, a neurotransmitter believed to be responsible for balancing mood. People with SAD had 5% more SERT, a protein that assists with serotonin transport, in the winter months than in summer. SERT transports serotonin from the synaptic clef to the presynaptic neuron, so higher SERT levels lead to lower serotonin activity, thus causing depression. Throughout the summer, sunlight generally keeps SERT levels naturally low. But as sunlight diminishes in the fall, a corresponding decrease in serotonin activity also occurs. Symptoms include: social withdrawal, increased need for sleep, weight gain and daily feelings of sadness, hopelessness, or unworthiness. Seasonal depression may get worse as the season progresses and can lead to suicidal thoughts(Melrose, 2015).

1.2.3.4.5 Post-partum Depression (PPD)

Also known as perinatal depression. This type of depression includes major and minor depressive episodes that occur during pregnancy or in the first 12 months

after delivery. Perinatal depression affects up to one in seven women who give birth and can have devastating effects on the women, their infants, and their families. (Merz, 2017).

1.2.3.4.6 Psychotic Depression

Psychotic depression is more severe form of depression, which is characterized by usually consistent of non-bizarre nihilistic, somatic, or guilty delusional beliefs and less often hallucinations. (Ozdemir *et al.*, 2015).

1.2.3.5 Treatment of Depression

1.2.3.5.1 Medications

Including antidepressants, mood stabilizers and antipsychotic medications.

1.2.3.5.2 Psychotherapy

Including cognitive behavioral therapy, family-focused therapy and interpersonal therapy.

1.2.3.5.3 Brain stimulation therapies

Including electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS).

1.2.3.5.4 Light therapy

Which uses a light box to expose a person to full spectrum light and regulate the hormone melatonin.

1.2.3.5.5 Exercise

1.2.3.5.6 Alternative therapies

Including acupuncture, meditation, and nutrition.

1.2.3.5.7 Self-management strategies and education

1.2.3.5.8 Mind/body/spirit approaches

Such as meditation, faith, and prayer (National Alliance on Mental Illness, 2015).

1.2.4 Blood

1.2.4.1 Definition of Blood

Blood is a unique fluid compromised of many cellular elements as well as a liquid portion consisting of proteins, amino acids, carbohydrates, lipids and elements (Lazarus and Schmaier, 2012).

1.2.4.2 Functions of Blood

-**Transportation and distribution:** Oxygen is carried from the lungs to the tissue and back CO2 from tissue to the lungs. Also carries nutrients to all parts of the body. Can carried hormones from endocrine glands to the body tissues and carries vitamins and enzymes.

-**Regulatory functions:** Regulation of blood pressure, body temperature, PH and fluid balance.

-Protective functions: Phagocytosis (ingestion and digestion of microorganism), production of antibodies and haemostatic function (Cheesbrough, 2006).

1.2.4.3 Hematopoiesis

It is the process of blood cell production, differentiation, and development. The hematopoietic system consists of the bone marrow, liver, spleen, lymph nodes, and thymus. Hematopoietic stem cells (HSCs) are the foundation of the adult hematopoietic system (Turgeon, 2012).

1.2.4.4 Stages of Hemopoiesis

1.2.4.4.1 Erythropoiesis

Under the influence of BFU hormone, Pluripotential stem give rise to BFU-E¸ they are most primitive erythroid progenitors.

Then give rise to CFU-E are most differentiated erythroid progenitor cells. Under the influence of erythropoietin hormone this cell gives rise to proerythroblast (rubriblast) (Turgeon, 2012).

1.2.4.4.2 Granulopoiesis

When the colony-forming-unit-granulocyte-erythrocyte-megakaryocyte (CFU-GEMM) progenitor cell differentiates into the colony-forming-unit-granulocyte-macrophage (CFU-GM) progenitor cell, the cell line becomes committed to developing into a myeloblast (Turgeon, 2012).

1.2.4.4.3 Thromopoiesis

These anuclear cells circulate in the peripheral blood after being produced from the cytoplasm of bone marrow megakaryocytes, the largest cells found in the bone marrow. Two classes of progenitors have been identified: the Burst -forming-unit megakaryocyte (BFU-M) and the Colony –forming-unit megakaryocyte (CFU-M).

The BFU-M is the most primitive progenitor cell committed to megakaryocyte lineage (Turgeon, 2012).

1.2.4.5 Complete Blood Count

The complete blood counts (CBCs) is one of the most commonly performed tests in health care. This is due to the vast amount of data obtained through the various components of this test. The test actually consists of several tests, which are: (Wilson, 2008)

1.2.4.6 Red Blood Cell (RBCs) Count

RBCs are a nucleate, biconcave, discoid cells fille4 with a reddish protein, hemoglobin (HG), which transports oxygen and carbon dioxide. It appear pink to red and measure 6 to 8 mm in diameter with a zone of pallor that occupies one third of their center, reflecting their biconcavity (Keohane et al., 2016).

Before the advent of reliable, automated electronic counting devices in the routine diagnostic laboratory, the red cell count were estimated visually in a haemocytometer on diluted samples of blood. The number of red cells that it is feasible to count under diagnostic laboratory conditions by 'the latter method is

insufficient to yield a highly reproducible value. For this reason, the red cell count was formerly rarely employed in clinical practice as an index of the adequacy, or otherwise, of red cells in the blood. Vastly greater numbers of red cells can be counted in a brief interval by currently available electronic devices, and the error in the red cell count is consequently reduced to an order comparable to, or even less than, that of the haemoglobin level (Frank, et al., 1996).

1.2.4.7 Hemoglobin (Hb)

Hemoglobin a complex molecule composed of four globin chains, each of which partially encloses a haem molecule, which has as its major function the transport of oxygen from the lungs to the tissues (Bain and Gupta, 2003).

1.2.4.7.1 Structure of Hemoglobin

Hemoglobin has a quaternary structure characteristic of many multi-subunit globular proteins (Van Kessel *et.al*, 2003). Most of the amino acids in hemoglobin form alpha helices, connected by short non-helical segments (Figure 1-2). Hydrogen bonds stabilize the helical sections inside this protein, causing attractions within the molecule, folding each polypeptide chain into a specific shape. Hemoglobin's quaternary structure comes from its four subunits in roughly a tetrahedral arrangement (Hoff brand *et. al*, 2006).

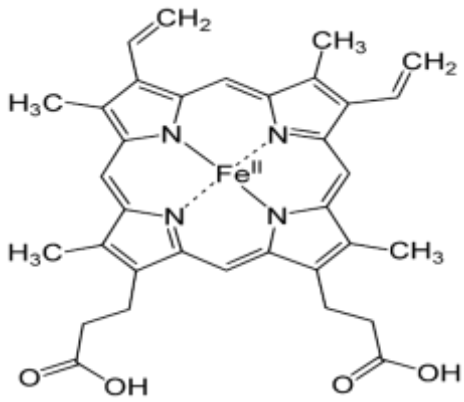


Figure (1-2): Structure of Haemoglobin (William, 2002).

1.2.4.7.2 Synthesis of Hemoglobin

Hemoglobin (Hb) is synthesized in a complex series of steps. The hem part is synthesized in a series of steps in the mitochondria and the cytosol of immature red blood cells, while the globin protein parts are synthesized by ribosome's in the cytosol. (Hoffbrand *et. al*, 2006). Figure 1-3.

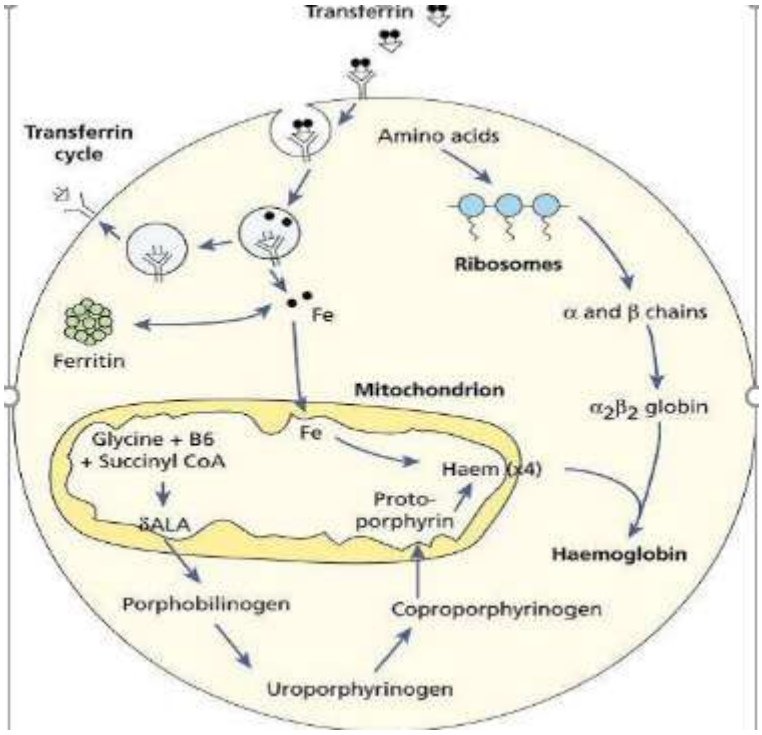


Figure (1-3): Synthesis of Haemoglobin (Hoffbrand *et. al*, 2006)

1.2.4.8 Hematocrit (HCT)

(or packed cell volume (PCV) is the proportion of blood volume occupied by red blood cells (Dacie and Lewis, 2006). it is done by centrifugation, or either by a

calculation based on the red cell count and average size of the red cells or using another technology, a quasi-direct measurement (Beck, 2009).

1.2.4.9 Leukocytes (WBCs)

The total WBCs is determined in whole blood in which red cells have been lysed. The lytic agent is required to destroy the red cells and reduce the red cell stroma to a residue that causes no detectable response in the counting system without affecting leucocytes in such a manner that the ability of the system to count them is altered (Dacie and Lewis, 2006). Sophisticated hematology analyzers produce the total WBC count and a five-part WBC differential (percentages and absolute numbers of each cell type). More attention is paid to the percent of each cell type, but the absolute number is really more relevant than the percent (Kern, 2002).

1.2.4.9.1 Neutrophils

This cell has a characteristic dense nucleus consisting of between two and five lobes, and a pale cytoplasm with fine pink-blue (azurophilic) or grey-blue granules (Hoffbrand *et al.*, 2006).

1.2.4.9.2 Eosinophil

Eosinophils which make up 1–4% of the peripheral blood leukocytes are similar to neutrophils but with somewhat more intensely stained reddish granules. The absolute of eosinophils is up to 400cell/μL. Eosinophilic cells can first be recognized at the myelocyte stage (Munker *et al.*, 2007).

1.2.4.9.3 Basophils

This cell has many dark cytoplasmic granules which overlie the nucleus and contain heparin and histamine. In the tissues they become mast cells. They have immunoglobulin E (IgE) attachment sites and their degranulation is associated with histamine release (Hoffbrand *et al.*, 2006).

1.2.4.9.4 Lymphocytes (“Lymphs”)

It ranges in size from large (17 to 20 mm) in younger cells to small (6 to 9 mm) in older cells. The nuclear-cytoplasmic N: C ratio ranges from (2:1) in younger cells to (4:1 to 3:1) in older cells. The nucleus is round or oval and may have an indentation (cleft) and the nucleoli are not visible.

The chromatin pattern is dense and appears clumped. The cytoplasm is light sky blue and very scanty. A few azurophilic granules may be present (Turgeon, 2012).

1.2.4.9.5 Monocytes (“Monos”)

It is the largest cell in peripheral blood, 20 to 40 mm in size; there is an ovoid nucleus, usually irregular in outline, with invaginations.

Chromatin has a patchy, streaky structure, which have dense, homogeneous nuclei.

The basophilic cytoplasmic stains a grayish color and contain a scattered population of very fine reddish granules (Theml *et al.*, 2004).

1.2.4.10 Platelet Count

The most important value to consider is the total platelet count. Hematology analyzers also give a mean platelet volume (MPV), analogous to the MCV. It has been suggested that larger platelets are more effective than smaller platelets; however, the MPV has generally not proven very useful (Kern, 2002).

1.2.4.11 Red Cell Indices

Red cell indices traditionally have been the derived parameters of MCV, MCH, and MCHC; more recently, red cell distribution width (RDW) has also been included and, for some instruments, haemoglobin distribution width (HDW). These indices are the basis for classifying anemias, and in various combinations they have been used to aid in the distinction between iron deficiency and thalassemia's (Lafferty *et. al*, 1996).

1.2.4.11.1 Mean Cell Volume (MCV)

This is a direct measurement on most instruments. It supplies only the average size of the red cells, and says nothing about the range or variation of their sizes (Beck, 2009) MCV is measured directly, but in semi-automated counters MCV is calculated by dividing the PCV by RBCs (femtoliters).The MCV has been used to guide the diagnostic workup in patients with anemia, for example testing patients with microcytic anemia for iron deficiency or thalassemia, 16 and those with macrocytic anemia for folate or vitamin B12 deficiency (Griner and Oranburg, 1978).

1.2.4.11.2 Mean Cell Haemoglobin (MCH)

Expresses the average weight (content) of hemoglobin in an average erythrocyte. It is directly proportional to the amount of hemoglobin and the size of the erythrocyte (Turgeon, 2012). The MCH, the amount of hemoglobin per red cell, is calculated by the formula MCH (pg/cell) = hemoglobin (g/dl) / red cell count (x 10^6 cells/L) x 10.The MCH increases or decrease as the does the MCV and generally provide little additional diagnostic information (Williams, 2002).

1.2.4.11.3 Mean cell Haemoglobin Concentration (MCHC)

Expresses the average concentration of hemoglobin per unit volume of erythrocytes. It is also defined as the ratio of the weight of haemoglobin to the volume of erythrocytes (Turgeon, 2012). The MCHC, the concentration of haemoglobin per unit with red cell volume, is calculated by the formula MCHC (g/dl of red cells) = hemoglobin (g/dl) / hematocrit (ml/100 dl) x 100. An MCHC greater than 35 g/dl red cells is associated with hereditary spherocytosis,23 and a low MCHC is typical of iron deficiency,24 but its diagnostic usefulness is limited (Mahu *et. al*,1990).

1.2.4.12 Mean Red Cell Distribution Width (RDW)

Which is a measurement of the variation in size of the RBCs, and attempts to give a figure to the degree of anisocytosis, this being a morphological term indicating how much the cells vary in size (Beck, 2009).

Table 1-1: Approximate Normal Blood Values (Dacie and Lewis, 2006)

Value	**Male**	**female**
Hemoglobin g/dl	13-18 g/dl	12-16 g/dl
PCV %	40-54%	37-47%
RBC 10^{12}/L	$4.7\text{-}6.1\times10^{12}$/L	$4.2\text{-}5.4\times10^{12}$/L
WBC 10^{9}/L	$4.0\text{-}10.0\times10^{9}$/L	
Platelet count 10^{9}/L	$145\text{-}400\times10^{9}$/L	
MCV(fl)	80-96 fl	
MCH (pg)	27-32 pg	
MCHC (g/dl)	32-36 g/dl	
RDW %	9.5–15.5%	
Neutrophils	36-75	
Lymphocytes	20-50%	
Monocytes	3-8%	
Eosinophils	0-5%	
Basophils	0-2%	

1.2.5 Anemia

Anemia is defined clinically as a blood hemoglobin or hematocrit value that is below the appropriate reference range for age and sex (Hoffbrand and Moss, 2016). The three major pathophysiological categories which causes anemia:

1. Blood loss
2. Impaired red cell production
3. Red cell destruction excess the ability of the marrow to replace these losses Clinical signs and symptoms of anemia can result from diminished delivery of oxygen to the tissues usual complaints of an anemic patient are fatigability and

dyspnea, vertigo, faintness, headache, heart palpitations, pallor, low blood pressure, a slight fever and some edema (Turgeon, 2012).

1.2.5.1 Anemia can classify based on the red cell indices in to:

1-Microcytic hypochromic anemia (Low MCV, MCHC).

Iron deficiency anemia (some), Thalassemia, Sideroblastic anemia

2-Normocytic normochromic (Normal MCV, MCHC)

Anemia of chronic disorders, autoimmune disease, Bone marrow disorder

3-Macrocytic normochromic (High MCV)

Vitamin B12 deficiency, Folate deficiency, Excessive alcohol ingestion, Hypothyroidism (Turgeon, 2012)

1.2.5.2 Anemia can classify based on the etiology:

1-Blood loss; acute blood loss and chronic blood loss

2-Impird production: Aplastic, Iron deficiency, Sideroblastic anemia, Anemia of chronic disease and Megaloblastic

3-Hemolytic: Inherited defects and acquired disorders

4-Hemolytic-Hemoglobine disorders (Turgeon, 2012)

1.2.6 Iron Deficiency Anemia

1.2.6.1 Iron Distribution in Body

The total body iron content of the normal adult depending on the sex and Weight and it increases roughly in proportion to body weight. . It is varies from 3.to 5 g. It is greater in males than in females.it is distributed in Hemoglobin, Storage (available) tissue iron (ferritin and hemosiderin) Essential (non-available) tissue iron (myoglobin and enzymes of cellular respiration).Plasma (transport) iron (Firkin *et al*., 2008).

1.2.6.2 Iron Role in Body

Iron is essential for many metabolic processes. it is required for the production of red blood cells (a process known as erythropoiesis), but it's also part of hemoglobin (that is the pigment of the red blood cells) binding to the oxygen and thus facilitating its transport from the lungs via the arteries to all cells throughout the body. Iron is also necessary for the function of ribonucleotide reductase, a key enzyme in DNA synthesis. (Hoffbrand,A.V., *et al* 2005).

Also it is essential for proper growth and functioning of the nervous system, particularly important in childhood and pregnancy. (Swaminathan *et al.*, 2016).

The immune system is dependent on iron for its efficient functioning and physical (Scientific Advisory Committee on Nutrition, 2010) .

1.2.6.3 Iron Absorption

There are two oxidative forms, ferrous (Fe+2) and ferric (Fe+3) iron. Iron is absorbed as Fe2+ in the proximal duodenum by the divalent metal transporter 1(DMT1). Dietary Fe^{+3} must be reduced to Fe^{+2} by a duodenal ferric reductase - Dcytb (duodenal cytochrome b) - before its transport via DMT-1. In the enterocyte, iron may be stored as ferritin or be transferred to plasma through the basolateral membrane. Normally, iron is stored in mucosal cells. In cases of iron deficiency or increased erythrocyte production, mucosal cells produce little ferritin and most iron entering the cell is available for transport through the basolateral membrane. The Fe^{+2} transporter through the basolateral membrane was identified by three transmembrane glycoprotein called ferroportin or IREG-1 or MTP1 which are located in polarized basolateral membrane cells and expressed in the duodenum, placenta (iron transport from mother to embryo), liver Kupffer cells (iron recycling), spleen, macrophages and kidney. Hephaestin is a multicopper protein acts as an intracellular ferroxidase to facilitate iron.

Oxidation for fast binding with plasma transferring and delivery to cells that express transferring receptors.(Souza, 2005).

1.2.6.4 Storage Form of Iron

The human body stores iron in two forms. The total amount of body iron stores is around 600 to1000 mg in the normal adult male and around 200 to 300 mg in the normal adult female. Storage areas include liver, spleen, marrow, duodenum, skeletal muscle and other anatomic areas. (Saito, 2014).

1.2.6.4.1 Ferritin

It is iron-containing proteins which is invisible by photomicroscopy or may be faintly visible and stained diffusely in the tissue cells by Prussian blue, if concentrated.it is water-soluble and heat-resistant up to 75°C. The amount of ferritin iron is slightly larger than hemosiderin iron in the range from iron deficiency to normal. (Saito, 2014).

1.2.6.4.2 Hemosiderin

It is iron-containing proteins which is yellow-brownish granules that can be stained by Prussian blue in the tissue cells.it is water-insoluble and thermally denatured. The amount of hemosiderin iron becomes larger than ferritin
Iron in the iron overload range (Saito, 2014).

1.2.6.5 Iron Supply to the Tissues

1.2.6.5.1 Serum iron and iron-binding capacity

The serum iron and, more particularly, the saturation of the total iron-binding capacity of transferrin (TIBC) give a measure of the iron supply to the tissues. A reduced serum iron concentration with a normal or reduced TIBC is a characteristic response to infection and inflammation. (Hoffbrand,A.V., *et al* 2005).

1.2.6.6 Iron Transportation

1.2.6.6.1 Transferrin

Transferrin is a β-globulin, synthesized primarily in the liver. (Henry, 1991). It is protein responsible for iron transport. Transferrin transports ferric ions from the iron stores of intracellular or mucosal ferritin to bone marrow where erythrocyte precursors and other cells have transferrin surface receptors. Transferrin is responsible for 50% to 70% of the iron binding capacity of serum. (Jacobs *et al*, 1996). It is increase in case of iron deficiency and with increased estrogen due to pregnancy, oral contraceptives. (Tietz, 1995). It is decreased In case of chronic liver disease, malnutrition, nephrotic syndrome, and protein-losing enteropathies, iron overload due to multiple transfusion or hereditary hemochromatosis, and congenital atransferrinemia. (Burtis and Ashwood, 1994).

1.2.6.7 Pathophysiology of Iron Deficiency Anemia

When increased demand of iron the first step is to depletion of body stores, which are mobilized for hemoglobin Production, iron absorption is increase before anemia develop, serum iron is normal but ferritin is fallen.

With further iron depletion, when the serum ferritin is below 15 µg/L, the serum transferrin saturation falls to less than 15% due to a rise in transferrin concentration and a fall in serum iron. This leads to the development of iron-deficient erythropoiesis and increasing concentrations of serum transferrin receptor and red cell protoporphyrin with normal MCV and MCH.

Iron deficiency anemia develops if negative balance continues. The red cells become obviously microcytic and hypochromic, and poikilocytosis becomes more marked. The MCV and MCH are reduced. The reticulocyte count is low for the degree of anemia. The serum TIBC raises and the serum iron falls. When iron deficiency is severe and chronic, widespread tissue changes may be present, including koilonychia (ridged nails, breaking easily), angular stomatitis

(especially in those with badly fitting dentures), glossitis (hair thinning) and pharyngeal webs (Paterson–Kelly syndrome). Gastric atrophy may also predispose to iron deficiency. Pica is sometimes present; in some who eat clay or chalk; this may be the cause rather than the result of iron deficiency. Iron-dependent enzymes in the tissues are usually better preserved than other iron-containing compounds. In severe iron deficiency, however, these enzymes are not inviolate and their levels may fall. Infants with iron deficiency anemia may have impaired mental development and function. (Hoffbrand.A.V, *et al* 2005).

1.2.6.8 Clinical Features of Iron Deficiency Anemia

General symptoms and signs of anemia and also a painless glossitis, angular stomatitis, ridged or spoon nails (koilonychia) and unusual dietary cravings (pica). The cause of the epithelial cell changes is not clear but may be related to reduction of iron-containing enzymes. In children, iron deficiency can cause irritability, poor cognitive function and a decline in psychomotor development. (Hoffbrand and Moss, 2016)

1.2.6.9 Causes of Iron Deficiency

1-Decrease iron intake: Iron deficient diets

2-Increase iron utilization: Postnatal growth spurt and Adolescent growth spurt

3-Iron loss (physiology): Menstruation and Pregnancy

4-Incomplete iron absorption: Autoimmune gastritis, Celiac disease and H. pylori infection

5- Iron loss (pathological): GI bleeding, urogenital bleeding, pulmonary hemosiderosis, intravascular hemolysis, Malignancy (e.g., colon cancer) (Turgeon, 2012)

1.2.6.10 Laboratory Findings

Complete blood count shows hemoglobin, hematocrit, MCV, MCH, MCHC are below than normal range (Hoffbrand.A.V., *et al* 2005). Blood film shows hypochromic, microcytic cells with occasional target cells and pencil-shaped poikilocytes .The reticulocyte count is low in relation to the degree of anemia Bone marrow examination shows complete absence of iron from stores (macrophages) and from developing erythroblasts (Hoffbrand and Moss, 2016).

Iron profile finding Serum iron, Serum ferritin, transferrin Saturation Significant decrease, transferrin and TIBC are Increase (Turgeon, 2012).

1.2.7 Relation between Iron Deficiency Anemia and Depressive Disorders

Depressive Disorder (DD) is one of the most common mental disorders worldwide. Etiology of depressive disorder is broadly classified into two major categories, i.e. non-modifiable (genetic) and modifiable (environmental). Nutrition is an important modifiable etiological factor. Iron deficiency anemia (IDA) is the most common nutritional deficiency that affected most of people in developing countries. Decreased productivity, decreased academic performance, immune system disorders and neural dysfunction in vulnerable groups is adverse consequences of IDA. No such specific causative relation has yet been established between iron deficiency and DD. However, there are some facts that force us to consider this factor. The clinical presentation of patients, affected by iron deficiency anemia (IDA), often mimics that of depressive disorder, such as lethargy, irritability and behavioral disturbances. Iron has an important role in neurologic functions and developments. Iron is a cofactor for a number of enzymes involved in neurotransmitter synthesis, such as tryptophan hydroxylase (Serotonin) and tyrosine hydroxylase (norepinephrine and dopamine). Patient with iron deficiency anemia the iron supplementation leads to improvement in depressive symptoms even before any visible improvement in RBC count or

other indicators is observed. It seems that this phenomenon is due to the recovery of neurotransmitters and enzyme levels, dependent on iron, unrelated to hemoglobin (Hb) concentration.(Sciences, Sciences and Practitioner, 2015; Shafi *et al.*, 2018).

1.3 Previous Studies

Cross-sectional study was conducted by Noorazar SGh, et al in 2010-2011 at clinics of Tabriz University of Medical Sciences, Iran. Convenience sampling was used to select 100 women diagnosed with MDD, according to psychiatric diagnosis and Hamilton depression rating scale (HDRS) and also HDRS was used for evaluation of depression severity. Blood samples were taken for complete blood count difference analysis and evaluating anemia and in those with hemoglobin (Hb) < 12 mg/dl, ferritin, and total iron binding capacity were checked to evaluate IDA. Patients mean age was 36.34 ± 10.43 years old. Mean HDRS score was 32.20 ± 4.07. From which 19 had anemia, and among them 8% had IDA. Mean HDRS score in patients with IDA (33.37 ± 1.90) was higher than those without (32.09 ± 4.19), but the difference was not significant (P = 0.39). The relationship between blood sample indicators with HDRS scores, and there were not any significant association. There is no significant association between depressive symptoms and serum ferritin levels. There was no difference between patients with and without anemia in HDRS score. The negative relation was observed between Hb levels, and HDRS score (Pearson correlation = -0.21, P = 0.03) .HDRS scores were the higher in unmarried patients compared with married patients and in married patients was higher compared with divorced or widowed patients. However, the difference between groups Were not statistically significant (P = 0.70). There is negative correlation between Hb level and HDRS score in total patients, anemic patients, and IDA group, and it demonstrate the effect of Hb decrease and anemia on depression severity. (Noorazar SGh *et al.*, 2015).

A prospective, longitudinal, community-based study conducted by Lee et al. included 337 participants (108 men and 229 women; age range, 38-87 years) who received evaluations of MCHC, hemoglobin levels and depressive symptom

scores (DSS) during baseline and follow-up examinations, which were performed in 2008-2011 and 2010-2012, respectively. MCHC and hemoglobin levels were measured as part of complete blood counts, while DSS was evaluated using the Beck Depression Inventory. Associations were analyzed using linear regression. They found a statistically significant association between baseline MCHC and follow-up DSS ($\beta = -0.69$, $p = 0.026$), which remained statistically significant after controlling for potential confounders ($\beta = -0.71$, $p = 0.011$). Further, when they analyzed the relationship separately for men and women, they observed that it remained stable for women before ($\beta = -1.00$, $p = 0.014$) and after ($\beta = -1.09$, $p = 0.003$) adjusting for confounders. The stable association indicates that MCHC may be superior to hemoglobin level as a prognostic factor for future depressive symptoms in women. (Lee *et al.*, 2017).

A cohort study was conducted by Lever-van Milligen et al, aimed to which extent hemoglobin levels are associated with depression and anxiety disorders in a large cohort. the study sample consisted of 2920 persons from the Netherlands Study of Depression and Anxiety. Hemoglobin levels were determined after venipuncture. Depressive and anxiety disorders were determined according to a DSM-IV-based psychiatric interview. Clinical psychiatric characteristics included the severity of depression and anxiety, the duration of symptoms, the age of onset and the antidepressant use. Higher hemoglobin levels were found in those with current depressive and/or anxiety disorders after socio demographic adjustment and both higher, and lower hemoglobin levels were found in persons with higher depression and anxiety severity. However, after full adjustment for socio demographics, disease indicators and lifestyle, associations were no longer significant. This cohort study showed that there is no independent association between depressive and/or anxiety disorders and hemoglobin levels or anemia status. (Lever-van Milligen *et al.*, 2014).

Another cross-sectional study conducted by Chen et al. involved 180 participants recruited from a veterans' home in Northern Taiwan. For each case, the clinical research assistant performed an extensive examination, including a diagnostic structured interview with the Mini-International Neuropsychiatric Interview (MINI), the Geriatric Depression Scale (GDS-15), the Clinical Dementia Rating Scale (CDR), and cognitive tests, including the Cognitive Abilities Screening Instrument Chinese version (CASI C-2.0) test, and the Wechsler Digit Span Task test (Forward and Backward), blood samples were taken for Hb measurement. Cognitive function test showed that the mean total CASI score was 85.3±6.6 (range = 68–98). Hb concentrations ranged from 6.1 to 17.3 g/dL, with an average of 13.5 g/dL (SD = 1.8 g/dL). Mean scores for GDS-15, Digit Span Forward test, Digit Span Backward test and CDR were 2.9 (SD = 2.7), 11.4 (SD = 3.0), 3.4 (SD = 2.1) and 0.1 (SD = 0.2), respectively. Pearson's correlation tests demonstrated that Hb concentrations negatively correlated with GDS-15 ($r = -0.245$, $P = 0.001$) but did not correlate with Cognitive Abilities Screening Instrument, Forward or Backward Digit Span tests. Lower Hb levels, therefore, were associated with depression in the elderly men. (Chen, Yeh and Tsai, 2012).

Also, a cross-sectional study was conducted by Yi et al in July and November 2006 among employees working in two municipal offices in northeastern Kyushu, Japan. Involved 528 participant, 312 men and 216 women. Depressive symptoms were assessed by using a Japanese version of the Center for Epidemiologic Studies Depression scale (CES-D), blood sample was taken for measured serum ferritin concentrations. 36.5% of men and 36.1% of women had a CES-D scale score of ≥16. The prevalence of those with a CES-D score of ≥19 and ≥23 was 26.0% and 14.4% for men and 26.4% and 14.4% for women, respectively. Mean values of serum ferritin concentrations were significantly

higher in men (Mean=163.9 μg/L, S.D. =141.9) than in women (Mean=49.7 μg/L, S.D. =59.9) (pb0.001).In women, those aged 50 years or older had significantly higher levels of serum ferritin concentrations (Mean=38.6 μg/L, S.D. =50.7) compared to those aged younger than 50 years (Mean = 77.6 μg/L, S.D. = 71.8) ($p<0.001$). This study concluded that depressive symptoms, as assessed by CES-D (with a cutoff of ≥19), were associated with decreased levels of serum ferritin concentrations in apparently healthy men suggest that adverse mental health effects may be implicated in iron deficiency in Japanese workers. (Yi *et al.*, 2011).

Another Cross-sectional study conducted by Su et al to examine the relationship between serum ferritin and depressive symptoms among 3,839 subjects who were from the Tianjin Chronic Low-grade Systemic Inflammation and Health (TCLSI Health) cohort. Depressive symptoms were assessed using the Chinese version of 20-item self-rating Depression Scale (SDS) with 4 cutoffs (40, 45, 48 and 50) to indicate elevated depressive symptoms (40 was the primary cut-off). The prevalence of depressive symptoms was 36.5%, 17.6%, 11.0% and 7.0% for SDS ≥40, ≥45, ≥48 and ≥50, respectively. With the primary cut off point of 40, multiple potential confounding factors were adjusted and the odds ratios (95% confidence interval) of having elevated depressive symptoms by quartiles of serum ferritin concentrations were 1.00 (reference), 1.10 (0.91, 1.34), 0.81 (0.66, 1.01) and 1.02 (0.81, 1.28) for the first, second, third and fourth quartile, respectively (P for trend = 0.76). Similar relations were observed with the use of other cut-offs as a definition of depressive symptoms. The assessment of depressive symptoms was performed in 4 cut-offs (40, 45, 48, and 50) and no significant association was found in crude and Age-, Sex- and BMI adjusted and multiple-adjusted models with any cut-off. In conclusion, the study shows that

there is no significant association between serum ferritin concentrations and depressive symptoms among Chinese adults.(Su *et al.*, 2016).

A Cross sectional study conducted by Onder et al. data from the ‘‘Invecchiare in Chianti’’ (Aging in the Chianti area) study, a prospective population-based study of older people living in the community includes 1156 participants aged 65 years and older who were randomly selected. Details on blood sampling are reported elsewhere. Anemia was defined by the World Health Organization (WHO) criteria: hemoglobin concentration below 12 g/dl in women and below 13 g/dl in men. Depressive symptoms were measured by using the Center for Epidemiological Studies Depression Scale (CES-D). Participants with a CES-D score >16 were considered to be depressed. Mean age of the 986 participants was 75 years, and 56% were female; 313 (32%) study participants were depressed. Anemia was recorded in 48 of the 313 (15%) participants with depression and in 53 of the 673 (8%) participants without depression ($p<.001$). After adjusting for potential confounders, depression was associated with a significant higher risk of anemia (odds ratio = 1.93; 95% confidence interval, 1.19–3.13). The risk of anemia progressively and significantly increased with increasing CES-D score (signifying more severe depression). Compared with non-depressed participants (CES-D score, 16), the odds ratio for anemia were 1.74, 2.04, and 2.10 for participants with mild (score=16–20), moderate (score=21–26), and severe depression (score. 26), respectively (p for linear trend=.01). This study concludes that depressive symptoms are associated with anemia in a general population of older persons living in the community. (Onder *et al.*, 2005).

A case control study conducted by Shafi et al, in period from January to July 2017 at Sindh Rangers Hospital, Karachi, involved 100 Cases were selected on uniformly accepted criteria as diagnosed patients of depressive disorder and equal number of age and gender matched controls. Symptoms of depressive

disorders were assessed on HAM-D rating scale, and Blood samples were taken for Hemoglobin (Hb) level and peripheral film from both groups. Median Hb levels were 11.9 for depressed patients versus 12.9 for healthy participants. Significant difference between Hb levels of two groups was found ($p<0.001$), i.e. depressed participants were found to have higher frequency of anemia (73%) as compared to non-depressed participants (16%, $p=0.001$). Spearman rank correlation coefficient for Hb level and depression was -0.429 ($p<0.01$), showing significant negative correlation. The odds for Hb level were 0.487 (0.37-0.64), which showed that cases are less likely to be found with higher Hb levels as compared to controls ($p<0.001$). This study concludes that there is relationship between iron deficiency anemia and depressive disorder; and severity of symptoms of DD increases with degree of IDA. (Shafi *et al.*, 2018).

A Cross-sectional data were analyzed from 1875 participants 65 years and older who had participated in the 2005 Health Survey for England. Serum hemoglobin (Hb), ferritin, and transferrin receptor levels and depressive symptoms (Geriatric Depression Scale) had been measured. Depressive symptoms were associated with anemia (Hb <12.0 g/dL for women and <13.0 g/dL for men; present in 10.8%; odds ratio [OR] = 1.53 [95% confidence interval = 1.08-2.18]) after adjustment for age, sex, social class, multivitamin intake, smoking status, and body mass index, but this association was reduced substantially after further adjustment for physical health status (OR = 1.14). Low serum ferritin level (<45 ng/mL; present in 21.6%) was associated with depressive symptoms after full adjustment (OR = 1.37 [95% confidence interval = 1.03-1.81]). Linear models, however, revealed significant associations between higher number of depressive symptoms and lower Hb level and higher serum transferrin receptor level but not with ferritin levels. (Stewart and Hirani, 2012).

Another case control study conducted by Shariatpanaahi et al, in period from 2004–2005 at Free University of Medical Science in Tehran involved a hundred and ninety-two female medical students. The students were grouped as depressed and healthy (67 depressed students and 125 healthy controls). Hemoglobin (Hgb) level, serum ferritin, ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), folic acid, vitamin B12 and Hgb simultaneously had been measured. The prevalence of depression in the study population was 34.7%. The mean ferritin level in students with depression was significantly lower than the healthy ones ($P<0.001$). By changing the status from normal ferritin level to low ferritin level, odds of depression was increased by 1.92 ($P<0.05$). The study implies a possible association between depression and decreased ferritin level before the occurrence of anemia.(Shariatpanaahi *et al.*, 2007).

1.4 Rationale and Objectives

1.4.1 Rationale

Iron deficiency anemia is one of the most serious health problems in Sudan and around the world. More than 700 million people in the world suffer from low blood iron hemoglobin levels in daily food intake specially the pregnant women and children are the most vulnerable to anemia mainly in developing countries. Many complications arise from this type of anemia, some research has concluded that iron deficiency anemia may lead to depressive disorder. A great deal of evidence has shown that iron is an important component in cognitive, sensorimotor, and social-emotional development and functioning, because the development of central nervous system processes is highly dependent on iron. Furthermore, multiple studies have shown that the degree of iron deficiency affects the symptoms of depressive disorders. So, iron study is essential to confirm the iron deficiency anemia in a depressed patient, this can management the severity of depressive disorders by iron supplement before become more complicated. Thus, the aim of this research is to evaluate of complete blood count and iron profile among Sudanese patients with depressive disorders.

1.4.2 Objectives

1.4.2.1 General objective:

• To assist complete blood count and iron profile among Sudanese patients with depressive disorders

1.4.2.2 Specific Objectives:

- To measure complete blood count parameters in patients with depressive disorders.
- To measure serum iron, serum ferritin, total iron binding capacity and transferrin saturation in patients with depressive disorders.
- To compare mean concentration of hematological parameters with reference value.
- To compare mean concentration of hematological parameters with severity of depressive disorders.
- To associate the severity of depressive disorders with low hemoglobin level.
- To associate the severity of depressive disorders with iron deficiency anemia.
- To associate the severity of depressive disorders with demographic factors.
- To associate the severity of depressive disorder with medications.
- To associate the severity of depressive disorder with RBCs/PLT/WBCs morphology.

Chapter Two

Materials and Methods

2.1 Study Design, Area and Duration

This is a cross sectional study, conducted in Military hospital and Tejani Almahi for psychiatric disorders hospital at Omdurman, Sudan during the period from August 2019 to October 2019.

2.2 Sample Size

The study concerned a group of 50 patients with depressive disorders.

2.3 Inclusion Criteria

Sudanese patients known diagnosed to have depressive disorder were included in this study.

2.4 Exclusion Criteria

Chronic medical disorders (such as chronic liver disease, chronic renal disorders, hypothyroidism and hyperthyroidism), acute disorder, other psychiatric disorders, women who were pregnant or were in postpartum period.

2.5 Sample Collection

Venous blood samples (3ml) were collected in Ethylene diamine tetra acetic acid (EDTA) containers for complete blood count (CBC), peripheral blood picture (PBP), and (2ml) collected in plain containers for Iron profile investigation.

2.6 Materials Required

-Blood analyzer.

-Ethylene diamine tetra acetic acid (EDTA) blood containers.

-Syringes.

-Tourniquet.

-Alcohol swabs.

-cotton.

-slides.

-stain.

2.7 Blood Analyzer

Mindray BC 3000plus analyzer was used RBCs/PLTs/WBCs counting and for hemoglobin measurement.

2.7.1 Principle of Blood Analyzer

2.7.1.1 RBC/PLT/WBC measurement

RBCs/PLTs/WBCs were counted and sized by the impedance method. This method was based on the measurement of changes in electrical resistance produced by a particle, which in this case was a blood cell, suspended in a conductive diluent as it passes through an aperture of known dimensions. An electrode was submerged in the liquid on both sides of the aperture to create an electrical pathway. As each particle passed through the aperture, a transitory change in the resistance between the electrodes was produced and due to this a measurable electrical pulse was produced. The number of pulses generated indicated the number of particles that passed through the aperture. The amplitude of each pulse was proportional to the volume of each particle. Each pulse was amplified and compared to the internal reference voltage channels, which only accepted the pulses of a certain amplitude. If the pulse generated was above the RBC/PLT lower threshold, it was counted as an RBC/PLT, and if the pulse generated was above the WBC threshold, it was counted as a WBC, but before the WBC were counted a lyse was added to lyse the RBC (Mindray manual).

2.7.1.2 Hemoglobin (Hb) measurement

Hemoglobin **(Hb)** was determined by the colorimetric method. The WBC/Hb dilution was delivered to the WBC bath where it is bubble mixed with a certain amount of lyse, which converts hemoglobin to a hemoglobin complex that is measurable at 525 nm. An LED was mounted on one side of the bath and emits a beam of light, which passes through the sample and a 525nm filter, and then was measured by a photo-sensor that was mounted on the opposite side. The signal

was then amplified and the voltage was measured and compared to the blank reference reading. (Readings taken when there is only diluent in the bath). The Hb was calculated per the following equation and expressed in g/L.

Hb (g/L) = Constant ×Log 10 (Blank Photocurrent/Sample Photocurrent). (Mindray manual).

2.7.2 Procedure of Blood Analyzer

The instrument was checked up for making sure that the waste container was empty, that there were enough reagents, and also checked for the tubing and power connections. Then the power key was pressed on, present the mixed sample to the sample probe and press the aspirate key, the analysis progress was displayed on the screen and when the analysis was finished, the result was displayed on the screen and then you can print it out (Mindray manual).

2.8 Method of Preparation and Staining of Blood Films

2.8.1 Preparation of blood Film

A small drop of blood was placed in the center line of a slide about 1 cm from one end. Then, without delay, place a spreader in front of the drop at an angle of about 30 degrees to the slide and move it back to make contact with the drop. The drop should spread out quickly along the line of contact. With a steady movement of the hand, spread the drop of blood along the slide. The spreader must not be lifted off until the last trace of blood has been spread out. The film should be labeled immediately after spreading (Bain *et al*., 2011).

2.8.2 Staining of Blood Film (RALs Stain)

2.8.2.1 Kits Components

-Bottle (1): Fixative-RAL555 X 100ml.

-Bottle (2): Eosin-RAL555 X 100ml.

-Bottle (3): Blue-RAL555 X 100ml. (Reactifs RAL, 2019).

2.8.2.2 Staining Procedure

the slide was dipped 10 seconds in solution 1 then the excess was drained into solution onto filter paper, then the slide was dipped 5 seconds in solution 2 and the excess solution was drained onto filter paper, then it was dipped in solution 3 for 10 seconds and the slide was briefly washed with distilled water and it was allowed to dry in the open air then the slide was examined under an x100-immersion-objective microscope (Reactifs RAL, 2019).

2.9 Iron Profile

Samples were collected in plain vacutainers and centrifuged to obtain serum.

The serum was analyzed using Tosoh AIA 1800 to obtain serum ferritin, and Cobas c 311 analyzer for serum iron and total iron binding capacity.

2.9.1 Serum Ferritin

2.9.1.1 Tosoh AIA 1800 Principle

The ST AIA-PACK FER is a two-site immune enzymometric assay, which was performed entirely in the AIA-PACK. Ferritin present in the test sample was bound with monoclonal antibody immobilized on a magnetic solid phase and enzyme-labeled monoclonal antibody in the AIA-PACK. The magnetic beads were washed to remove unbound enzyme labeled monoclonal antibody and were then incubated with a fluorogenic substrate, 4-methyl-umbelliferyl phosphate (4MUP). The amount of enzyme labeled monoclonal antibody that binds to the beads is directly proportional to the Ferritin concentration in the test sample. A standard curve was constructed, and unknown sample concentrations were calculated using this curve (Pribori.com, 2019)

2.9.1.2 Reference Value:

Children: 7---140µg/L

Men: 20 --- 250 µg/L

Women: 20 --- 200 µg/L

2.9.2 Serum iron and Total iron binding capacity (TIBC)

2.9.2.1 Principle of Cobas c 311 analyzer

The Roche Diagnostic Cobas C311 analyzer is fully automated, software-controlled analyzer for clinical chemistry analysis. It is designed for both quantitative and qualitative in vitro determinations using a large variety of tests for analysis. The cobas C311 analyzer performs photometric assays and ion-selective electrode measurements and uses serum/plasma. (Gundersen health, 2019). Iron is an in vitro test for the quantitative determination of iron in human serum and plasma on Roche/Hitachi Cobas c systems.

Under acidic conditions, iron was liberated from transferrin. Lipemic samples were clarified by the detergent. Ascorbate reduces the released Fe3+ ions to Fe2+ ions which then react with Ferrozine to form a colored complex. The color intensity was directly proportional to the iron concentration and was measured photometrically.

The Total Iron Binding Capacity was calculated as follows:

TIBC = Total Iron + UIBC (Gundersen health, 2019).

2.9.2.2 Reagents/Materials

R1 Citric acid; thiourea and detergent.

R3 Sodium ascorbate; Ferrozine and preservative. (Gundersen health, 2019).

2.9.2.3 Reference value:

2.9.2.3.1 Serum iron

Male: 65 --- 175 µg/dL = 11.6 --- 31.3 mmol/L

Female: 40 --- 160 µg/dL =7.16 --- 26.85 mmol/L

2.9.2.3.2 Total iron binding capacity (TIBC)

200 --- 400 µg/dL =36 --- 72µmol/L

2.9.3 Transferrin Saturation

Transferrin saturation was calculated from TIBC and SI by formula.

Transferring saturation % = (Serum iron / total iron binding capacity) ×100

2.9.3.1 Reference value

20% --- 50%

2.10 Data Collection

The data for this study was collected by direct interview of the participants after their agreement, using pre designated questionnaire.

2.11 Ethical Approval

This study was approved from Sudan University for Science and Technology Ethical Committee, an Informed Consent was taken from every participant in this study before the sample was taken.

2.12 Data Analysis

Collected data was analyzed by statistical package for social sciences (SPSS) version (16).

Results was expressed as mean SD, One sample t test and chi square test of two-tailed p value was used to measure the significance of association between the values.

Chapter Three

Result

Results

This is a cross-sectional study carried out in Omdurman in the period from August 2019 to October 2019 to evaluate complete blood count and iron profile among 50 Sudanese patients diagnosed with depressive disorders according to psychiatric diagnosis also the signs and symptoms were used for evaluation of depression severity. Their age ranged (from 15 to 60) years old, divided in to 4 groups, 23 of them from (15 to 29) years which were (46%), 18 of them from (30 to 44) years (38%), 17 of them from (45 to 59) years which were (14%) and 2 of them above 60 years representing (4%). Fifty blood samples were collected from depressed patients and they were analyzed using automated blood analyzer (Mindry BC 3000plus), Tosoh AIA 1800 and Cobas c 311 analyzer.

Then the results were collected and the data was analyzed using SPSS version (16). The results were represented by the following figures and tables:

Table (3-1): Comparison of hematological parameters among depressed patients with reference values:

Blood Parameters	Mean± STD	Reference value		
		male	female	PV
Hb	13.2±1.84	13-18 g/dl	12-16 g/dl	.000
RBCs	4.75±0.57	4.7-6.1×10^{12}/L	4.2-5.4×10^{12}/L	.000
HCT	42.44±5.48	40-54%	37-47%	.000
MCV	89.33±8.24	80-96 fl		.259
MCH	27.73±2.93	27-32 pg		.000
MCHC	31.11±2.04	32-36 g/dl		.000
PLTs	227.64±84.38	145-400×10^{9}/L		.000
WBCs	5.51±2.10	4.0-10.0×10^{9}/L		.000
Neutrophil	2.93±1.65	2-8 ×10^{9}/L		.000
Lymphocyte	2.09±0.58	2-4 ×10^{9}/L		.000
Mix	0.51±0.39	0-1×10^{9}/L		.748
Serum iron	16.47±8.84	11.6-31.3 mmol/L	7.16-26.85 mmol/L	.033
Ferritin	89.97±78.75	20 --- 250 µg/L		.000
TIBC	60.02±23.56	36 --- 72 µmol/L		.077
Transferrin saturation	27.96±13.09	20% --- 50%		.000

Test showed significant result in all hematological parameters compared with reference values except MCV, Mix, and TIBC which give insignificant results.

Table (3-2): Comparison of hematological parameters among depressed patients with severity of depression:

Hematological parameters	Mild		Moderate		Sever		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**PV**
RBC	4.785	0.497	4.770	0.555	4.703	0.736	0.927
WBC	4.784	1.389	5.933	2.390	5.825	2.309	0.211
PLT	209.412	76.122	217.143	58.668	271.833	119.089	0.109
HB	13.341	1.346	13.633	1.690	12.333	2.467	0.142
HCT	42.959	5.057	43.286	5.542	40.250	5.842	0.283
MCV	90.153	8.869	90.390	6.111	86.317	10.377	0.354
MCH	27.959	2.593	28.419	2.316	26.233	3.928	0.111
MCHC	31.147	2.102	31.510	1.955	30.358	2.075	0.302
Neutrophil	2.429	0.948	3.329	1.973	2.958	1.764	0.254
Lymphocyte	1.935	0.649	2.095	0.534	2.325	0.556	0.216
mix	0.429	0.465	0.624	0.397	0.458	0.231	0.271
TIBC	59.100	15.990	63.105	31.932	55.958	14.481	0.699
Serum iron	16.122	5.195	17.390	11.262	15.389	8.679	0.812
Transferrin saturation	30.412	13.807	27.286	12.838	25.669	13.067	0.610
Ferritin	68.625	53.234	114.373	97.943	77.533	63.688	0.170

Test showed insignificant result in all hematological parameters compared with severity of depression.

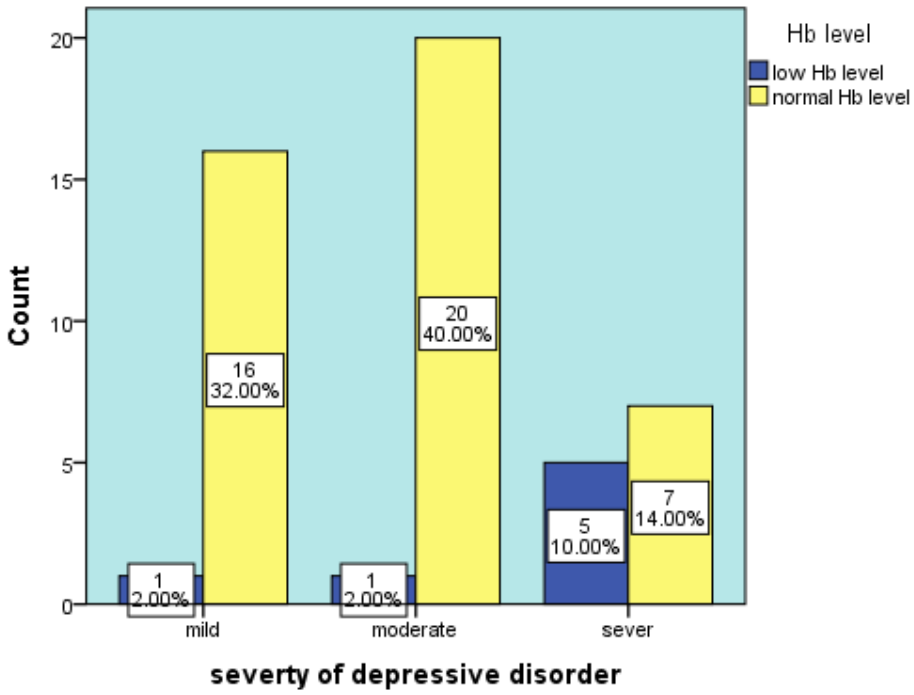


Figure (3-1): association between severity of depression and low Hb level

Test showed the patients who have normal Hb level represented highest percentage in moderate depression 40% while the low Hb level patient's represented highest percentage in severe depression 10%.

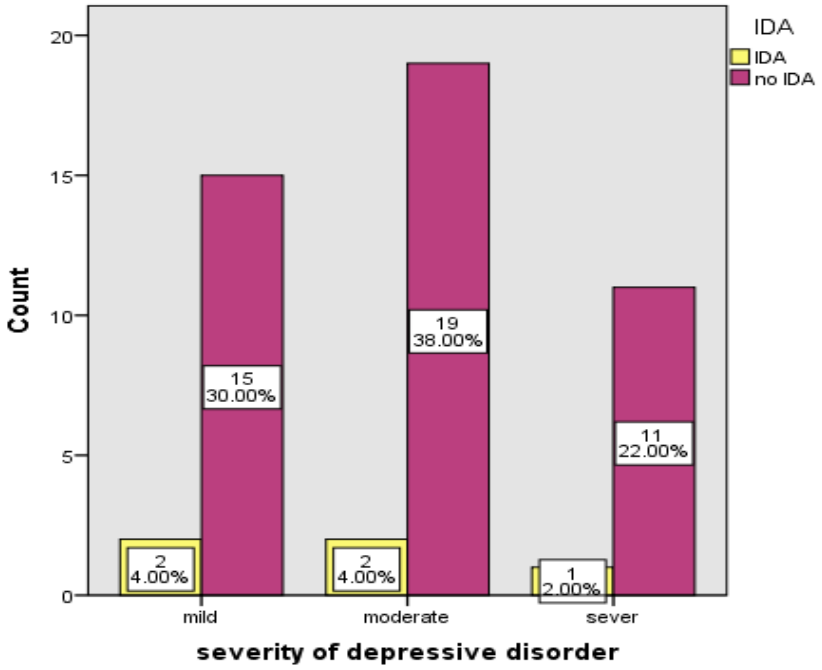


Figure (3-2): association between severity of depression and iron deficiency anemia

Test showed the patients who have no IDA represented highest percentage in moderate depression 38% while the IDA patient's represented highest percentage in mild and moderate depression 4%.

Table (3-3): Association between severity of depression and age

Age group	Depression Severity			**Total**
	Mild	Moderate	Sever	
15 - 29	11	6	6	23
	64.7%	28.6%	50.0%	46.0%
30 - 44	3	10	5	18
	17.6%	47.6%	41.7%	36.0%
45 - 59	2	4	1	7
	11.8%	19.0%	8.3%	14.0%
60+	1	1	0	2
	5.9%	4.8%	0.0%	4.0%
Total	17	21	12	50
	100.0%	100.0%	100.0%	100.0%
PV= 0.361				

Test showed the highest percentage in mild and severe depression in age group (15 – 29) which was represented 64.7% and 50% respectively while the highest percentage in moderate depression in age group (30–44) which represented 41.7%.

Table (3-4): Association between severity of depression and gender

			Depression Severity			Total
			mild	moderate	sever	
gender	male	Count	10	15	5	30
		% within depressive	58.8%	71.4%	41.7%	60.0%
	female	Count	7	6	7	20
		% within depressive	41.2%	28.6%	58.3%	40.0%
Total		Count	17	21	12	50
		% within depressive	100.0%	100.0%	100.0%	100.0%
PV= 0.243						

Test showed 60% were male while female represent 40% of total depressed patients, 71% from male have the highest percentage in moderate depression while the highest percentage from female is 58.3% in severe depression.

Table (3-5): Association between severity of depression and marital status

			Depression Severity			Total
			mild	moderate	sever	
marital status	single	Count	11	10	5	26
		% within depressive	64.7%	47.6%	41.7%	52.0%
	married	Count	6	11	7	24
		% within depressive	35.3%	52.4%	58.3%	48.0%
Total		Count	17	21	12	50
		% within depressive	100.0%	100.0%	100.0%	100.0%
PV= 0.412						

The study found that 52% were single while the married represented 48 % of total depressed patients, 64.4% from single patients have the highest percentage in mild depression while 58.3% from the marred patients have the highest percentage in severe depression.

Table (3-6): Association between severity of depression and socio economic status

			Depression Severity			Total
			mild	moderate	sever	
Socioeconomic status	low<2000	Count	1	5	4	10
		% within depressive	5.9%	23.8%	33.3%	20.0%
	Middle (2000-5000)	Count	9	9	6	24
		% within depressive	52.9%	42.9%	50.0%	48.0%
	upper >5000	Count	7	7	2	16
		% within depressive	41.2%	33.3%	16.7%	32.0%
Total		Count	17	21	12	50
		% within depressive	100.0%	100.0%	100.0%	100.0%
PV= 0.347						

The study found that 20% were low<2000, middle (2000-5000) represented 48% and they constitute the highest number from mild moderate and severe depression (52.9, 42.9, 50%) respectively, while the upper >5000 represent 32% of total depressed patients.

Table (3-7): Association between severity of depression and medication

			Depression Severity			Total
			mild	moderate	sever	
medication	olanzapine	Count	2	2	1	5
		% within depressive	11.8%	9.5%	8.3%	10.0%
	sertraline	Count	2	4	0	6
		% within depressive	11.8%	19.0%	0.0%	12.0%
	Na valproate	Count	1	0	1	2
		% within depressive	5.9%	0.0%	8.3%	4.0%
	cipram	Count	0	2	2	4
		% within depressive	0.0%	9.5%	16.7 %	8.0%
	no medication	Count	8	9	6	23
		% within depressive	47.1%	42.9%	50.0 %	46.0%
	olanzapine and cipram	Count	1	1	1	3
		% within depressive	5.9%	4.8%	8.3%	6.0%
	sertraline and olanzapine	Count	3	1	1	5
		% within depressive	17.6%	4.8%	8.3%	10.0%
	Olanzapine , sertraline , Na valproate	Count	0	1	0	1
		% within depressive	0.0%	4.8%	0.0%	2.0%
	Na valproate , olanzapine	Count	0	1	0	1
		% within depressive	0.0%	4.8%	0.0%	2.0%
Total		Count	17	21	12	50
		% within depressive	100.0 %	100.0%	100.0 %	100.0 %
PV= 0.802						

The study found that 46% of total depressed patients did not take medication and they constitute the highest number from the mild, moderate and severe depression (47.1, 42.9, 50%) respectively, 12% of total depressed take sertraline, 10% take olanzapine while 10 % take sertraline with olanzapine.

Table (3-8): Association between severity of depression and RBC morphology:

			Severity			Total
			mild	moderate	sever	
RBC. morphology	Normocytic normochromic	Count	15	20	8	43
		% within depressive	88.2%	95.2%	66.7%	86.0%
	Microcytic hypochromic	Count	1	1	1	3
		% within depressive	5.9%	4.8%	8.3%	6.0%
	Microcytic hypochromic with few eliptocyte	Count	0	0	2	2
		% within depressive	0.0%	0.0%	16.7%	4.0%
	Normocytic normochromic with few macrocytic	Count	1	0	0	1
		% within depressive	5.9%	0.0%	0.0%	2.0%
	Normocytic normochromic with many spherocyte and crenate cell	Count	0	0	1	1
		% within depressive	0.0%	0.0%	8.3%	2.0%
Total		Count	17	21	12	50
		% within depressive	100.0%	100.0%	100.0%	100.0%
PV= 0.137						

The result showed the normocytic normochromic picture represented the highest percentage of total 86% and they constitute the highest number from the mild, moderate and severe depression (88.2, 95.2, 66.7%) respectively, microcytic hypochromic represent 6%, microcytic hypochromic with few eliptocyte represent 4%, normocytic normochromic with few macrocytic represented 2%, normocytic normochromic with many spherocyte and crenate cell represent 2%.

Table (3-9): Association between severity of depression and platelet morphology:

			Depression Severity			Total
			mild	moderate	sever	
PLT. morphology	Adequate	Count	15	21	11	47
		% within depressive	88.2%	100.0%	91.7%	94.0%
	Thrombocytosis	Count	0	0	1	1
		% within depressive	0.0%	0.0%	8.3%	2.0%
	Thrombocytopenia	Count	2	0	0	2
		% within depressive	11.8%	0.0%	0.0%	4.0%
Total		Count	17	21	12	50
		% within depressive	100.0%	100.0%	100.0%	100.0%
PV= 0.126						

The result showed the adequate platelets represented the highest percentage of total 94% and they constitute the highest number from the mild, moderate and severe depression (88.2, 100, 91.7%) respectively, thrombocytosis represent 2% while thrombocytopenia represent 4%

Table (3-10): Association between severity of depression and WBC morphology:

			Depression Severity			Total
			mild	moderate	sever	
WBC. morphology	Normal	Count	15	20	11	46
		% within depressive	88.2%	95.2%	91.7%	92.0%
	Leukopenia	Count	1	0	1	2
		% within depressive	5.9%	0.0%	8.3%	4.0%
	Relative lymphocytosis	Count	1	0	0	1
		% within depressive	5.9%	0.0%	0.0%	2.0%
	Neutrophil leukocytosis	Count	0	1	0	1
		% within depressive	0.0%	4.8%	0.0%	2.0%
Total		Count	17	21	12	50
		% within depressive	100.0%	100.0%	100.0%	100.0%
PV= 0.553						

The result showed the normal WBC morphology represented the highest percentage of total 92% and they constitute the highest number from the mild, moderate and severe depression (88.2, 95.2, 91.7%) respectively, Leukopenia represent 4% , Relative lymphocytosis represent 2% and Neutrophil leukocytosis represent 2%.

Chapter Four

Discussion, Conclusion and Recommendations

Discussion, Conclusion and Recommendations

4.1 Discussion

The current study is a cross-sectional study carried out in Omdurman in the period from August 2019 to October 2019 to evaluate complete blood count and iron profile among 50 Sudanese patients diagnosed with depressive disorders according to psychiatric diagnosis also the signs and symptoms were used for evaluation of depression severity and classify in to mild, moderate and severe. Their age range (from 15 to 60) years old, divided in to 4 groups, 23 of them from (15 to 29) years which were (46%), 18 of them from (30 to 44) years (38%), 17 of them from (45 to 59) years which were (14%) and 2 of them above 60 years representing (4%). The results showed that the mean of CBC parameters and iron profile were normal as shown in table (1-3).

The results of the study showed that the mean of Hb concentration was significant in depressed patients compared with mean of the reference value [13.2±1.84 vs. 15 g/dl] (P.value= 0.000).

The mean of RBCs count was significant in depressed patient compared with mean of the reference [4.75±0.57vs. 5.15×10^{12}/L] (P.value =0.000).

The mean of Hemocrit was significant in depressed patients compared with mean of the reference value [42.44±5.48vs. 45.5%] (P.value 0.000).

The mean of MCV was insignificant in depressed patients compared with mean of the reference value [89.33±8.24vs. 88 fl] (P.value 0.259).

The mean of MCH and the MCHC concentration is significant in depressed patients compared with mean of the reference value [27.73±2.93 vs. 29.5 pg] (P.value 0.000) and [31.11±2.04vs. 34 g/dl] (P.value 0.000) respectably.

The mean of Platelet count was significant in depressed patients compared with mean of the reference value [227.64±84.38 vs. 272.5×10^{9}/l] (P.value 0.000).

The mean of WBCs count was significant in depressed patients compared with mean of the reference value [5.51±2.10 vs. 7×10^9/l] (P.value 0.000)

The mean of WBCs absolute count was significant in depressed patients compared with mean of the reference value; Lymphcyte [2.09±0.58vs. 3×10^9/L] (P.value 0.000), Neutrophil [2.93±1.65 vs. 5×10^9 /L] (P.value 0.000), while insignificant with mix [0.51±0.39 vs. 0.5×10^9/L] (P.value 0.748).

The mean of serum iron concentration was significant in depressed patients compared with mean of the reference value [16.47±8.84vs. 40.46×1012/l] (P.value 0.033).

The mean of ferritin concentration was significant in depressed patients compared with mean of the reference value [89.97±78.75vs. 135 µg/L] (P.value 0.000).

The mean of TIBC was insignificant in depressed patients compared with reference value [60.02±23.56vs. 90 µmol/L] (P.value 0.077).

The mean of transferrin saturation was significant in depressed patients compared with mean of the reference value [27.96±13.09 vs. 35%] (P.value 0.000).

The results of the study showed that the mean of Red blood cell count was insignificant in depressed patients compared with severity of depression [4.78±0.49 vs. 4.77± 0.55 vs. 4.70± 0.73 $\times10^{12}$/L] (P. value =0.927)

The mean of Hemoglobin concentration was insignificant in depressed patients compared with severity of depression [13.34±1.34 vs. 13.63± 1.69 vs. 12.33± 2.46 g/dl] (P. Value =0.142) which agreed with (Lever-van Milligen *et al.*, 2014) but disagreed with (Shafi *et al.*, 2018) ,(Stewart and Hirani, 2012) ,(Chen, Yeh and Tsai, 2012) and (Noorazar SGh *et al.*, 2015)

The mean of Hematocrit was insignificant in depressed patients compared with severity of depression [42.95±5.05 vs. 43.28± 5.54 vs. 40.25± 5.84 %] (P.value =0.283) which agree with (Noorazar SGh *et al*., 2015).

The mean of Mean cell volume was insignificant in depressed patients compared with severity of depression [90.15±8.86 vs. 90.39± 6.11 vs. 86.31± 10.37 fl] (P. value =0.354) which agreed with (Noorazar SGh *et al*., 2015).

The mean of Mean cell hemoglobin and the mean of Mean cell hemoglobin concentration were insignificant in depressed patients compared with severity of depression [27.95±2.5 vs. 28.41± 2.31 vs. 26.23± 3.92 pg.] (P. value =0.111) and [31.14±2.10 vs. 31.51± 1.95 vs. 30.35± 2.75 g/dl] (P. value =0.302) respectively. Which agreed with (Noorazar SGh *et al*., 2015) and disagreed with (Lee *et al*., 2017).

The mean of Platelet count was insignificant in depressed patients compared with severity of depression [209.4±76.1 vs. 217.1± 58.7 vs. 271.8± 119.1 $\times 10^{12}$/L] (P. value =0.109) respectively.

The mean of White blood cell count was insignificant in depressed patients compared with severity of depression [4.78±1.38 vs. 5.93± 2.39 vs. 5.82± 2.30 $\times 10^{12}$/L] (P. value =0.211).

The mean of serum iron was insignificant in depressed patients compared with severity of depression [16.12±5.19 vs. 17.39± 11.26 vs. 15.38± 8.67 mmol/L] (P. value =0.812). which agreed with (Noorazar SGh *et al.*, 2015).

The mean of total iron binding capacity was insignificant in depressed patients compared with severity of depression [59.10±15.99 vs. 63.10± 31.93 vs. 55.95± 14.48 µmol/L] (P. value =0.699). Which agree with (Noorazar SGh *et al*., 2015)

The mean of ferritin was insignificant in depressed patients compared with severity of depression [68.62±53.23 vs. 114.37± 97.94 vs. 77.53± 63.68 µg/L] (P. value =0.170). which agreed with (Noorazar SGh *et al*., 2015) , (Stewart and

Hirani, 2012)and (Su *et al.*, 2016) but disagreed with(Yi *et al.*, 2011) and (Shariatpanaahi *et al.*, 2007).

The mean of transferrin saturation was insignificant in depressed patients compared and severity of depression [30.41±13.80 vs. 27.28± 12.83 vs. 25.66± 13.06 %] (P. value =0.610).

The association between severity of depression and age groups showed the highest percentage in mild and severe depression in age group (15 – 29) which was represented 64.7% and 50% respectively while the highest percentage in moderate depression in age group (30–44) which represented 41.7%. (P. Value = .361) there was no relation between severity of depression and age. Which agreed with (Su *et al.*, 2016).

According to the gender the test showed 60% were male while female represent 40% of total depressed patients, 71% from male have the highest percentage in moderate depression while the highest percentage from female is 58.3% in severe depression. (P. Value = .243) there was no relation between severity of depression and gender. Which agreed with (Su *et al.*, 2016).

According to the marital status the study found that 52% were single while the married represented 48 % of total depressed patients, 64.4% from single patients have the highest percentage in mild depression while 58.3% from the marred patients have the highest percentage in severe depression, (P. Value = .412) there was no relation between severity of depression and marital status. Which agreed with (Noorazar SGh *et al*., 2015).

According to the socioeconomic status the study found that 20% were low<2000, middle (2000-5000) represented 48% and they constitute the highest number from mild moderate and severe depression (52.9, 42.9, 50%) respectively, while the upper >5000 represent 32% of total depressed patients. (P. Value = .347) there was no relation between severity of depression and socioeconomic status.

Referring to the medications the study found that 46% of total depressed patients did not take medication and they constitute the highest number from the mild, moderate and severe depression (47.1, 42.9, 50%) respectively, 12% of total depressed take sertraline, 10% take olanzapine while 10 % take sertraline with olanzapine. (P. Value = .802) there was no relation between severity of depression and medications.

According to peripheral blood picture the result showed the normocytic normochromic picture represented the highest percentage of total 86% and they constitute the highest number from the mild, moderate and severe depression (88.2, 95.2, 66.7%) respectively, microcytic hypochromic represent 6%, microcytic hypochromic with few eliptocyte represent 4%, normocytic normochromic with few macrocytic represented 2%, normocytic normochromic with many spherocyte and crenate cell represent 2%. (P. Value = .137) there was no relation between severity of depression and RBCs comment.

According to peripheral blood picture the result showed the adequate platelets represented the highest percentage of total 94% and they constitute the highest number from the mild, moderate and severe depression (88.2, 100, 91.7%) respectively, thrombocytosis represent 2% while thrombocytopenia represent 4%.(P. Value = .126) there was no relation between severity of depression and platelet comment.

The association between severity of depression and low hemoglobin level was significant (P. Value= 0.007) which shows the patients who have normal Hb level represented highest percentage in moderate depression 40% while the low Hb level patient's represented highest percentage in severe depression 10%, which agree with (Shafi *et al.*, 2018)and (Onder *et al.*, 2005) but disagreed with (Lever-van Milligen *et al.*, 2014).

The association between severity of depression and iron deficiency anemia was insignificant (P. Value= 0.951) which showed the patients who have no IDA represented highest percentage in moderate depression 38% while the IDA patient's represented highest percentage in mild and moderate depression 4%, which agreed with (Yi *et al.*, 2011) but disagreed with (Shafi *et al.*, 2018).

The discrepancy between our study and other studies that do not agreed with may be due to sample differences, ethnic differences or different depression rating.

4.2 Conclusion

Our findings indicate that normal complete blood count and iron profile noted in majority of depressed patient with statistical significant in all hematological parameters except MCV, Mix, and TIBC which statistical insignificant in depressed patients when compared with mean of reference values, and there is a relation between low hemoglobin level and depressive disorders while there is no relation between iron deficiency anemia, socio-demographic factors with severity of depressive disorders.

4.3 Recommendations

After completion of the study, the following were recommended:

1 HAM-D or other scale rather than signs and symptoms would be used for determine severity of depressive disorders.
2 Using Case control study design instead of cross sectional study.
3 Further studies using lager sample size needed for more accurate results.

Reference

Referencing

adaa.org (2019). Anxiety and Depression Association of America (Online) available at https://adaa.org/sites/default/files/Depression-ADAA_Brochure-2016 [accessed 22. Oct. 2019]

American Psychiatric Association. (2000). Treatment Works: Major Depressive Disorder: A Patient and Family Guide. American Psychiatric Pub..

Anisman, H., Merali, Z. and Poulte, M. O. (2012) 'Gamma-Aminobutyric acid involvement in depressive illness interactions with corticotropin-releasing hormone and serotonin', in The Neurobiological Basis of Suicide. CRC Press/Taylor & Francis.

Australian Government Department of Health and Ageing (2014) 'What is a depressive disorder?', Commonwealth of Australia. Available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/mental-pubs-w-whatdep.

Baghai, T. C., Eser, D. and Möller, H.-J. (2008) 'Effects of different antidepressant treatments on the core of depression', Dialogues in clinical neuroscience. Les Laboratoires Servier, 10(3), p. 309.

Bain, BJ and Bates, I. (2011). Approach to the diagnosis and classification of blood diseases, in: Bates, I., Bain, BJ.,Laffan, MA. And Lewis, SM. 11th edition, Dacie and Lewis practical heamatology. London: Churchill Livingstone, p3

Bain, BJ. And Gupta, R. (2003). A–Z of Hematology. Oxford: Blackwell Science Ltd, P 117, 179.

Beard, J. (2003) 'Iron deficiency alters brain development and functioning', The Journal of nutrition. Oxford University Press, 133(5), pp. 1468S-1472S.

Beard, J. L., Erikson, K. M. and Jones, B. C. (2002) 'Neurobehavioral analysis of developmental iron deficiency in rats', Behavioural brain research. Elsevier, 134(1–2), pp. 517–524.

Beard, J. L., Wiesinger, J. A. and Connor, J. R. (2003) 'Pre-and postweaning iron deficiency alters myelination in Sprague-Dawley rats', Developmental neuroscience. Karger Publishers, 25(5), pp. 308–315.

Beck, N. (2009). Diagnostic Hematology. London: Springer, pp 23-24.

Belmaker, R. H. and Agam, G. (2008) 'Major Depressive Disorder'.

Benazzi, F. (2006) 'Various forms of depression', Dialogues in clinical neuroscience. Les Laboratoires Servier, 8(2), p. 151.

Burhans, M. S., Dailey, C., Wiesinger, J., Murray-Kolb, L. E., Jones, B. C., and Beard, J. L. (2006) 'Iron deficiency affects acoustic startle response and latency, but not prepulse inhibition in young adult rats', Physiology & behavior. Elsevier, 87(5), pp. 917–924.

Burtis CA, Ashwood ER (1994). Tietz textbook of clinical chemistry 2nd ed'. Philadelphia: Saunders. pp. 712–3.

Cheesbrough, M. (2006) District laboratory practice in tropical countries. Cambridge university press.

Chen, H., Yeh, H. and Tsai, S. (2012) 'Association of lower hemoglobin levels with depression, though not with cognitive performance, in healthy elderly men', Psychiatry and clinical neurosciences. Wiley Online Library, 66(4), pp. 367–369.

Chen, M. H. Chen, M. H., Tung-Ping Su, Ying-Sheue Chen, Ju-Wei Hsu, Kai-Lin Huang, and Wen-Han Chang. (2013) 'Association between psychiatric disorders and iron deficiency anemia among children and adolescents: A nationwide population-based study', BMC Psychiatry, 13, pp. 1–8. doi: 10.1186/1471-244X-13-161.

Chen, Q., Beard, J. L. and Jones, B. C. (1995) 'Abnormal rat brain monoamine metabolism in iron deficiency anemia', The Journal of Nutritional Biochemistry. Elsevier, 6(9), pp. 486–493.

Crowe, A. and Morgan, E. H. (1992) 'Iron and transferrrin uptake by brain and cerebrospinal fluid in the rat', Brain research. Elsevier, 592(1–2), pp. 8–16.

Dacie and Lewis. (2006) Practical Haematology 10th ed., Churchill Livingstone, an Imprint of Elsevier: 26-51.

Fekadu, N., Shibeshi, W. and Engidawork, E. (2017) 'Major Depressive Disorder: Pathophysiology and Clinical Management.', Journal of Depression and Anxiety, 06(01), pp. 1–7. doi: 10.4172/2167-1044.1000255.

Firkin, F., Chesterman, C., Rush, B., and Pennigton, D. (2008) De Gruchy's Clinical haematology in medical Practice. John Wiley & Sons.p37

Frank, F., Colincheste, R., David, P., and Bryan, R. (1996). Haematology in Medical Practice, 5th edition. India.

Goldberg, D. (2006) The 'NICE Guideline' on the treatment of depression, Epidemiologia e Psichiatria Sociale.

Griner, P.F., Oranburg, P.R. (1978). Predictive values of erythrocyte indices for tests of iron, folic acid, and vitamin B12 deficiency. Am J Clin Pathol , 70:74825.

gundersenhealth.org. (2019). Iron C311 - Gundersen Health System. (Online) Available at https://www.gundersenhealth.org/app/files/public/6601/Lab-Policies-Iron-C311-Lab-8821.pdf [Accessed 23.oct. 2019]

gundersenhealth.org. (2019). Cobas C311 Routine Operation. (Online) Available at https://www.gundersenhealth.org/app/files/public/6623/Lab-Policies-Cobas-C311-Routine-Operation-Lab-4014.pdf

Han, J., Day, J. R., Connor, J. R., and Beard, J. L. (2003) 'Gene expression of transferrin and transferrin receptor in brains of control vs. iron-deficient rats.' Nutritional neuroscience, 6(1), pp. 1–10.

healthline.com (2019). What Does Gamma Aminobutyric Acid (GABA) Do? (Online) available at https://www.healthline.com/health/gamma-aminobutyric-acid [accessed 22. Oct. 2019]

Henry, J. B. (1991) 'Clinical diagnosis and management by laboratory methods 18. ed', Philadelphia, PA: WB Saunders.p233

Heugten-Van Der Kloet, V. and van Heugten, T. (2015) 'The classification of psychiatric disorders according to DSM-5 deserves an internationally standardized psychological test battery on symptom level', Frontiers in psychology. Frontiers, 6, p. 1108.

Hoffbrand, A. V, Moss, P. A. H. and Pettit, J. E. (2006), Essential haematology. 5th ed. Oxford: Blackwell Publishing, pp.21– 20–27.

Hoffbrand, A. V. and Moss, P. A. H. (2016) 'Hoffbrand's Essential Haematology 7th edn'. John Wiley & Sons Ltd.

Hoffbrand, A. V., Catovsky, D. and Tuddenham, E. G. D. (2005) 'Postgraduate Haematology'. 2005'. Blackwell Publishing Ltd, Massachusetts, USA. . P26-27, 35.

Jacobs DS, DeMott WR, Grady HJ. (1996) 'Laboratory Test Handbook, 4th ed'. Hudson, OH: Lexi-Comp. p.209.

KeohaneE M.,Smith L J and Walenga Jeanine M. (2016).Rodak's Hematology Clinical Principles and Applications. 5th ed.Elsevier.

Kern, M. (2002). PDQ Hematology. Ontario: B .C. Decker Inc, P 12 and 20-21.

Körük, S. and Özabacı, N. (2018) 'Şema Terapinin Depresif Bozuklukların Tedavisindeki Etkililiği: Bir Meta-Analiz', Psikiyatride Guncel Yaklasimlar - Current Approaches in Psychiatry, 10(4), pp. 460–470. doi: 10.18863/pgy.361790.

Lafferty, J. D., Crowther, M.A., Ali, M.A. (1996). The evaluation of various mathematical RBC indices and their efficacy in discriminating between

thalassemic and non-thalassemic microcytosis. American Journal of Clinical Pathology; 106:201-295.

Lazarus, H. M. and Schmaier, A. H. (2012) Concise guide to hematology. Springer.

Lee, J. M., Nadimpalli, S. B., Yoon, J. H., Mun, S. Y., Suh, I., and Kim, H. C.(2017) 'Association between Mean Corpuscular Hemoglobin Concentration and Future Depressive Symptoms in Women', The Tohoku journal of experimental medicine. Tohoku University Medical Press, 241(3), pp. 209–217.

Leffingwell, R. C. (1931) 'Causes of Depression', Proceedings of the Academy of Political Science, 14(3), p. 3. doi: 10.2307/1172700.

Lever-van Milligen, B. A., Vogelzangs, N., Smit, J. H., and Penninx, B. W. (2014) 'Hemoglobin levels in persons with depressive and/or anxiety disorders', Journal of psychosomatic research. Elsevier, 76(4), pp. 317–321.

Lima, D. (2004) 'Bipolar disorder and depression in childhood and adolescence', Jornal de pediatria, 80(2 Suppl), pp. 11–20.

Lincoln, A., Woolf, V., Aldridge, L., Hemingway, E., Plath, S., Churchill, W., Leigh, V., Norton, E., Piersall, J., Duke, P., Dickens, C. (2010) 'What is a Depressive Disorder ?'. pp. 1–20.

Lozoff, B., Jimenez, E., Hagen, J., Mollen, E., and Wolf, A. W. (2000) 'Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy', Pediatrics. Am Acad Pediatrics, 105(4), pp. 51–e51.

Lozoff, B., Beard, J., Connor, J., Felt, B., Georgieff, M., and Schallert, T. (2006) 'Long-lasting neural and behavioral effects of iron deficiency in infancy', Nutrition reviews. Oxford University Press Oxford, UK, 64(suppl_2), pp. S34–S43.

Mahu, J.L., Leclercq, C., Suquet, J.P. (1990).Usefulness of red cell distribution width in association with biological parameters in an epidemiological survey of iron deficiency in children. Int J Epidemiology: 19:646.

Manual of mindray

Melrose, S. (2015) 'Seasonal Affective Disorder: An Overview of Assessment and Treatment Approaches', Depression Research and Treatment, 2015, pp. 1–6. doi: 10.1155/2015/178564.

Merali, Z., Du, L., Hrdina, P., Palkovits, M., Faludi, G., Poulter, M. O., and Anisman, H. (2004) 'Dysregulation in the suicide brain: mRNA expression of corticotropin-releasing hormone receptors and GABAA receptor subunits in frontal cortical brain region', Journal of Neuroscience. Soc Neuroscience, 24(6), pp. 1478–1485.

Merz, B. (2017) 'Six common depression types - Harvard Health', Harvard Health Publications. Available at: http://www.health.harvard.edu/mind-and-mood/six-common-depression-types.

Miller, J. L., Schaer, D. J. and Buehler, P. W. (2013) 'Cold Spring Harb Perspect Med Iron Deficiency Anemia: A Common and Curable Disease'. doi: 10.1101/cshperspect. 011866.

Ministry of Health Singapore (2004) 'MOH clinical practice guidelines on obesity.' Available at: https://www.moh.gov.sg/content/dam/moh_web/HPP/Doctors/cpg_medical/withdrawn/cpg_Obesity-Apr2004.pdf.

Munker, R., Hiller, E. Glass, J and Paquette, R. (2007). Modern Hematology Biology and Clinical Management. 2th edition. New Jersey: Humana Press Inc. P 10.

National Alliance on Mental Illness (2015) 'Nami depression', Depression.

Nelson, S. L. (2012) 'Major Depressive Disorder: Overview', Treatment and Recurrence Prevention.

Noorazar SGh, Ranjbar F, Nemati N, Yasamineh N and Kalejahi P. (2015) Relationship between severity of depression symptoms and iron deficiency anemia in women with major depressive disorder. J Anal Res Clin Med; 3(4): 219-24. Doi: 10.15171/jarcm.2015.034

Onder, G., Penninx, B. W., Cesari, M., Bandinelli, S., Lauretani, F., Bartali, B., and Ferrucci, L. (2005) 'Anemia is associated with depression in older adults: results from the InCHIANTI study', The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. Oxford University Press, 60(9), pp. 1168–1172.

Ozdemir, O., Ozdemir, P. G., Milanlioglu, A., Tapanci, Z., and Timucin, D. K. (2015) 'Is major depressive disorder with psychotic features more likely in elderly than adulthood?' Journal of Mood Disorders, 5(1), p. 3. doi: 10.5455/jmood.20140908060721.

Penninx, B. W., Milaneschi, Y., Lamers, F., and Vogelzangs, N. (2013) 'Understanding the somatic consequences of depression : biological mechanisms and the role of depression symptom profile', BMC Medicine. BMC Medicine, 11(1), p. 1. doi: 10.1186/1741-7015-11-129.

pribori.com, (2019). Tosoh bioscience. (Online) available at http://www.pribori.com/products/pdf/tosoh_reagent. [Accessed 23.oct. 2019]

Pużyński, S. (2002) 'Choroby afektywne nawracające', Psychiatria, (Mdd), pp. 343–415.

Ral. Diagnostic.com. (2019) Ral. 555 Staining kit. Available at http://www.Ral Diagnostic. [Accessed 23.oct.2019.]

Rao, R., Tkac, I., Townsend, E. L., Gruetter, R., and Georgieff, M. K. (2003) 'Perinatal iron deficiency alters the neurochemical profile of the developing rat

hippocampus', The Journal of nutrition. Oxford University Press, 133(10), pp. 3215–3221.

Sachdev, H. P. S., Gera, T. and Nestel, P. (2005) 'Effect of iron supplementation on mental and motor development in children: systematic review of randomised controlled trials', Public health nutrition. Cambridge University Press, 8(2), pp. 117–132.

Saito, H. (2014) 'Metabolism of iron stores', Nagoya journal of medical science. Nagoya University School of Medicine/Graduate School of Medicine, 76(3–4), pp. 235–236.

Salters-pedneault, B. K. (2019) 'Types of Psychiatric Disorders', pp. 4–7.

Sciences, B., Sciences, B. and Practitioner, G. (2015) 'Relationship between severity of depression symptoms and iron deficiency anemia in women with major depressive disorder', 3(4), pp. 219–220. doi: 10.15171/jarcm.2015.034.

Scientific Advisory Committee on Nutrition.(2010) 'Iron and Health'. The Stationery Office London. pp. 120-121

Setälä, T. A. (2002) Depressive Disorders Among, National Public Health Institute.

Shafi, M., Taufiq, F., Mehmood, H., Afsar, S., and Badar, A. (2018) 'Relation between depressive disorder and iron deficiency anemia among adults reporting to a secondary healthcare facility: A hospital-based case control study', Journal of the College of Physicians and Surgeons Pakistan, 28(6), p. 456. doi: 10.29271/jcpsp.2018.06.456.

Shariatpanaahi, M. V., Shariatpanaahi, Z. V., Moshtaaghi, M., Shahbaazi, S. H., and Abadi, A. (2007) 'The relationship between depression and serum ferritin level', European journal of clinical nutrition. Nature Publishing Group, 61(4), p. 532.

soterixmedical.com (2019). Depression tDCS-LTE™ System (Online) available at https://soterixmedical.com/depression/depression [accessed 22. Oct. 2019]

Souza, A. M. De (2005) 'Iron metabolism', 3(2), pp. 123–124.

Stass, S., Schumacher, H. and Rock, W. (2000) Handbook of hematologic pathology. CRC Press.

Stewart, R. and Hirani, V. (2012) 'Relationship between depressive symptoms, anemia, and iron status in older residents from a national survey population', Psychosomatic medicine. LWW, 74(2), p. 208.

Su, Q., Gu, Y., Yu, B., Yu, F., He, H., Zhang, Q., and Shi, H. (2016) 'Association between serum ferritin concentrations and depressive symptoms among Chinese adults: a population study from the Tianjin Chronic Low-Grade Systemic Inflammation and Health (TCLSIHealth) cohort study', PloS one. Public Library of Science, 11(9), p. e0162682.

Swaminathan, A., Kumarasamy, S., Shanmugam, S., Ayyavoo, S., and Velayutham, S. (2016) 'Motor nerve conduction parameters in patients with iron deficiency anemia', National Journal of Physiology, Pharmacy and Pharmacology, 6(6), p. 567. doi: 10.5455/njppp.2016.6.0617103072016.

Talmage (2018) 'A List of Psychological Disorders', Theories, p. 1. Available at: https://www.verywellmind.com/a-list-of-psychological-disorders-2794776.

Taylor, E. M., Crowe, A. and Morgan, E. H. (1991) 'Transferrin and iron uptake by the brain: effects of altered iron status', Journal of neurochemistry. Wiley Online Library, 57(5), pp. 1584–1592.

Theml, H., Diem, H. and Haferlach, T. (2004). Color Atlas of Hematology. 2th edition. New York: Thieme, p 46 and 50.

Tietz, N. W. (1995) 'Clinical guide to laboratory tests 3rd ed . WB Saunders Co Philadelphia', Pa, 186, p. 188.

Trivedi, J. K. and Kar, S. (2011) 'Focus issues in dysthymia', Neuropsychiatry. Future Medicine Ltd, 1(3), pp.291–297.

Turgeon, ML. (2012). Clinical Hematology Theory and Procedures. 5th edition. Philadelphia: Lippincott Williams &Wilkins, p 73, 79, 92-94,117,238-241,254,269,302 and 403.

Van, Kessel. et al. (2003). Proteins - Natural Polyamides." Chemistry 12.Toronto: Nelson .

Virginia Commission on Youth. (2017) 'Depressive disorders', pp. 1-17.

Willimam, F. Kern. (2002). PDQ heamatology first edition,USA,Decker publishing Ltd. P.22-25.

Wilson, DD. (2008). McGraw-Hill's Manual of Laboratory& Diagnostic Tests. New York: The McGraw-Hill Companies, p 177.

Yi, S., Nanri, A., Poudel-Tandukar, K., Nonaka, D., Matsushita, Y., Hori, A., and Mizoue, T. (2011) 'Association between serum ferritin concentrations and depressive symptoms in Japanese municipal employees', Psychiatry research. Elsevier, 189(3), pp. 368–372.

Appendices

بسم الله الرحمن الرحيم

Sudan University for Science and Technology
College of Graduate Studies

Questionnaire

(Evaluation of CBC and iron profile among Sudanese patients with depressive disorders)

1- Patient general date:

Patient ID:

1-Patient name: …….……..

2-Sample number: .…….……

3-Phone number: ……..…..

4-Age: …….

5-Gender: female …….. Male ……

6-Marital status: single ……. Married …….. Widowed ……. Separated ……

7-Resident:…….…….

8-Socioeconomic status (monthly income):

Low <2000 …… middle (2000-5000) …….. Upper >5000 ……..

9-Depressive disorder: mild …… moderate …… sever …….

2-Clinical date of patient:

Medication you take:

……

……

……

……

3- Laboratory date:

a- Complete blood count:	RBC	HTC	Neutrophil	basophil
	WBC	MCV	Lymphocyte	
	PLT	MCH	Monocyte	
	Hb	MCHC	eosinophil	
b- Peripheral blood picture :				

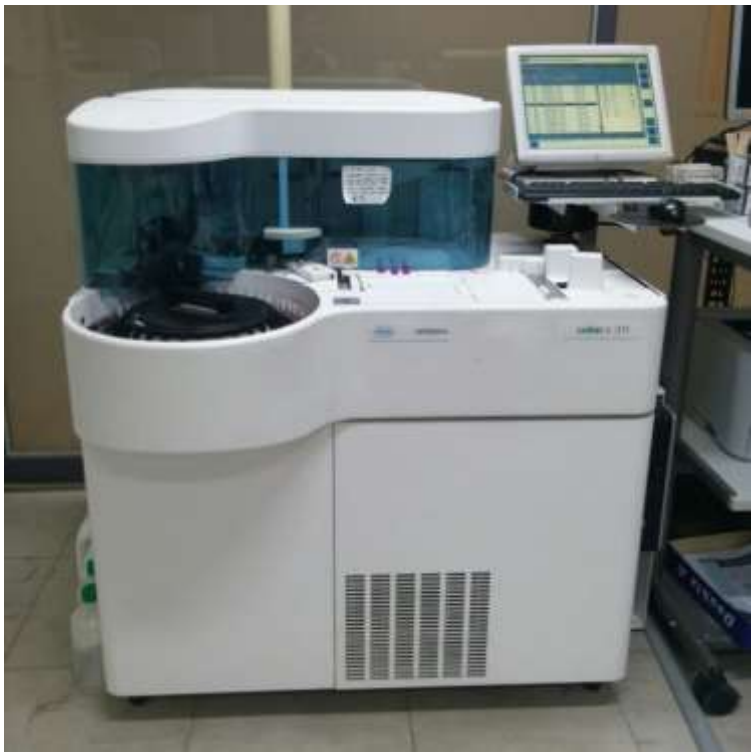
c- Iron profile :	Serum Transferrin	TIBC	Serum iron	Transferrin saturation	ferritin

4- Consent of patient :

I agree to participate in this research about the Evaluation of serum iron profile and CBC in Sudanese patients with depressive disorders. I accept to share the information regarding my health condition including the lab results and any other information that may help in this research.

Appendix: BC-3000 plus Auto Hematology Analyzer

Appendix: Tosoh AIA 1800



Appendix: Cobas c 311 analyzer