Chapter One

Introduction and literature review

Any one can develop a mental health issue, some mental disorders are mild; others are serious and longer-lasting, but all of them can be diagnosed and effectively treated. Most people go back to living their “normal” lives after treatment. Psychiatric medications are often an important element in the successful treatment of mental disorders (psych central 2014)Coronary artery disease (CAD) as well as depression is both highly prevalent diseases. Both cause a significant decrease in quality of life for the patient and impose a significant economic burden on society. There are several factors that seem to link depression with the development of CAD and with a worse outcome in patients with established CAD: worse adherence to prescribed medication and life style modifications in depressive patients, as well as higher rates in abnormal platelet function, endothelial dysfunction and lowered heart rate variability. The evidence is growing that depression is an independent risk factor for cardiac events in a patient population without known CAD and also in patients with established diagnosis of CAD, particularly after myocardial infarction. (Januzzi et al., 2000)

1.1 Classification of Plasma lipids

Lipids are soluble in organic solvent, but nearly water insoluble. Major lipids present in the plasma from endogenous or exogenous sources are fatty acids, Phospholipids, Triglycerides and Cholesterol. (Marshall and stephen 2004) Cholesterol is primarily composed of C-H bonds, and hence it is fairly water insoluble. It does, however, contain a polar hydroxyl (OH) group. Thus it is both a polar and non polar molecule (Amphipathic). (koolman and Roehm 2005)

It’s the major constituent of the cell membrane of animal cells. It would be possible for the body to provide its full daily cholesterol requirement by synthesizing it itself. However, with mixed diet, only about half of the cholesterol is derived from endogenous biosynthesis, which takes place in the intestine, skin and mainly in the liver (about 50%). The rest is taken up from food. Most of cholesterol is incorporated into the lipid layer of plasma membranes or converted into bile acid. A very small amount of cholesterol is used for biosynthesis of the steroid hormones. In addition; up
to 1 g cholesterol per day is released into the bile and thus excreted. (koolman and Roehm 2005)

Fatty Acids (RCOOH) is the general chemical formula for fatty acid, where “R” is an alkyl chain. Fatty acid chain length vary and are commonly classify as; short chain (2 to 4 carbon atoms), medium chain (6 to 10 carbon atoms), or long chain (12 to 26 carbon atoms) fatty acid. Those of important in human nutrition and metabolism are the long chain class. Fatty acids are further classified according to their degree of saturation. Saturated fatty acids have no double bonds between their carbon atoms; monounsaturated fatty acids contain one double bond; and polyunsaturated fatty acids contain multiple double bonds. Fatty acids exist in circulation in either an un-esterifies or free, the later primarily bound to albumin, or in various esterifies forms, such as triglycerides, phospholipids, or cholesterol esters. (Brutis et al 2008)

Triglycerides Is made up of fatty acids and glycerol and is partly synthesized in the liver hepatocyte. It is transported through the bloodstream by chylomicrons and very low density lipoproteins (VLDLs). Triglycerides provides energy to the cells as it loses its fatty acid and form ATP, thus acting as an energy store in the form of fat, and it insulates organs through fat deposits. (hubbard 2010)

Phospholipids formed by conjugation of two fatty acids and phosphorylated glycerol. Phospholipids make up the bi layer of cell membranes and also form a coating that surrounds cholesterol and triglycerides and glues them to lipoprotein core. (hubbard 2010)

1.2 Lipoproteins

Because lipids are not soluble they transported in the plasma associated with proteins. Albumin is the principle carrier of free fatty acids while other lipids circulate in complex known as lipoproteins. These complex of non-polar of triglycerides and cholesterol esters surrounded surface layer of phospholipids, cholesterol and protein known apolipoproteins. (Marshall and stephen 2004)

Lipoproteins are classified into five groups, in order of decreasing size and increasing density, these are: chylomicrons, VLDLs, low density lipoproteins (LDLs) and high density lipoproteins (HDLs). The proportion of apoproteins range from 1% in chylomicrons to over 50% in HDLs. These proteins serve less for solubility purpose, but rather function as recognition molecules for the membrane receptors and enzymes that are involved in lipid exchange. (koolman and Roehm 2005)
Chylomicrons are the largest of the lipoproteins particles. They are the major carries of exogenous triglycerides. Chylomicrons comprise 90 to 95% (by weight) triglycerides, 2 to 6% phospholipids, 2 to 4% cholesterol ester, 1% free cholesterol and 1 to 2% Apo-lipoproteins( Apo) C and B. Chylomicrons are responsible for transporting dietary triglyceride and some cholesterol to the rest of the body. The clearance times from the formation of chylomicrons after meal and the removal the remnants of the liver in about six hours. Normally, chylomicrons are not found in 12 to 14 hours fasting blood specimen. (Bishop et al., 2005)

Very low density lipoproteins VLDLs, like chylomicrons, are also rich in triglycerides and are major carrier of endogenous triglycerides. VLDLs comprise 50 to 65% (by weight) triglycerides, 8 to 14% cholesterol ester, 12 to 16% phospholipids, 4 to 7% free cholesterol and 5 to 10% Apo( B,C and E). Excess dietary intake of carbohydrate enhances hepatic synthesis of triglycerides, which in turn increase VLDL production. (Bishop et al., 2005)

Intermediate density lipoproteins are usually undetectable in normal plasma, it is normally transient intermediate lipoprotein formed during the conversion of VLDL to LDL. It contain both cholesterol and endogenous triglycerides (Bishop et al 2005)

Low density lipoproteins (LDL) contains 50% cholesterol by weight and is most cholesterol rich of the lipoproteins. They are synthesized in the liver and are responsible for transporting cholesterol from the liver to peripheral tissue LDL is the most atherogenic lipoproteins and high serum is regard as major Coronary Heart disease (CHD) risk factor. Lipoproteins of smaller size do not scatter light; even very high concentrations in plasma do not produce lipemia. Another lipoproteins, lipoprotein (a), similar in composition to LDL but has high protein content (contain one molecule of Apo (a) linked to Apo B-100 by a disulfide bond). Lipoprotein (a) is normally present in low plasma concentration, increase level lead to increased risk for premature coronary heart disorders and stroke by promoting clotting that lead to MI and stroke. (Bishop et al., 2005, Brutis et al., 1995)

High density lipoproteins HDLs are smallest lipoproteins. HDL particles are synthesis by both the liver and intestine. HDL typically carries 20 to 35 % of total plasma cholesterol, but unlike LDL, which carry cholesterol to the tissue, HDL take excess cholesterol from tissue to the liver (reverse transport) and sometimes referred to as the good cholesterol . Based on density differences there are two major groups of HDL
substances: HDL2 and HDL3. HDL2 is larger in size and richer in lipid than HDL3 and may be the efficient vehicle for transfer of cholesterol from the peripheral tissue to the liver. (Bishop et al 2005)

1.3 Lipids and Lipoproteins Metabolism

1.3.1 Exogenous pathway

Dietary triglyceride and cholesterol are absorbed in the intestine mucosa and incorporated to form the core of nascent chylomicrons, which are then transported to plasma. In peripheral tissue, chylomicrons interact with lipoprotein lipase, which removes most of core triglyceride from the lipoprotein particle. The resulting glycerol and fatty acids are taken up by adipose and other tissues, re-formed into triglyceride and stored. Redundant surface material (Apo C, phospholipids and cholesterol ester) joins the HDL particles. The remnant chylomicron particles, which are now smaller and enriched in their core with cholesterol ester and some remaining triglycerides, are taken up by the liver. This dietary cholesterol can then be used for bile acid formation, incorporated into membranes, re-secreted back into the circulation as lipoprotein cholesterol or excreted into bile as cholesterol. (Goldderg 2008)

1.3.2 Endogenous pathway

Triglyceride and cholesterol are also synthesized in the liver. This endogenous system, which conveys these lipids from liver to peripheral tissue and back to liver, is divided into two sub-system: the Apo B-100 lipoprotein system (VLDL-C, IDL and LDL-C) and Apo A-1 lipoprotein system (HDL-C). (Bishop et al 2005)

Apo B-100 lipoprotein system in the liver triglycerides and cholesterol are packed with apo B-100 and phospholipids to form VLDL. Once released into plasma, VLDL undergoes triglycerides removal by mean of lipoprotein lipase; the resulting cholesterol ester-rich remnants are the LDL. Unlike the chylomicrons remnants are the IDL. Can be converted by further triglycerides removal to even smaller and denser LDL. During this process the lipoprotein loses all its surface apo except apoB-100. (Goldderg 2008)

Apo A-1 lipoprotein system HDL, rich in apo A-1 which transport cholesterol from peripheral tissue to the liver. Cholesterol-poor HDL3 particles first form in plasma from coalescence of phospholipids-Apo complexes. Free cholesterol then transfer from cell membranes to HDL3, where it converts into cholesterol ester and enters the HDL core. The HDL3 can then accept more free cholesterol and become the larger
more cholesterol-rich HDL2 particles. HDL2 is then metabolized by one of two main pathways: transfer to apo B lipoproteins (which are subsequently removed by liver) by mean of cholesterol ester transfer protein or direct hepatic metabolism with removal of the HDL2 apoproteins from plasma. (Goldderg 2008)

1.4 Lipids and Lipoproteins Disorders
Diseases associated with abnormal lipid concentration are referred to as dyslipidemia. They can be cause directly by genetic abnormalities or through environmental/lifestyle imbalances or they can develop secondarily, as a consequence of other diseases. (Bishop et al., 2005)

1.4.1 Primary Hyperlipidemia
Common genetic polymorphisms of the many enzymes, structure proteins, and receptors involved in lipoprotein metabolism, collectively are thought to have a major impact on any individual’s tendency for developing dyslipidemia (Richard et al 2000)

1.4.2 Secondary Dyslipidemia
In many patients hyperlipidemia is caused by some underlying "non-lipid" etiology rather than a primary disorder of lipid metabolism. The secondary causes of dyslipidemia are: type 2 diabetes mellitus, excessive alcohol consumption, obstructive liver diseases, nephrotic syndrome, chronic renal failure, hypothyroidism, cigarette smoking, obesity, and drugs (corticosteroids therapy, orally administered estrogens and oral contraceptives pregnancy). (Vodnala, 2012)

1.4.3 Additional causes of Secondary Dyslipidemia
Causes follow Hypercholesterolemia: Acute intermittent porphyries (also associated with hypertriglyceridemia). High saturated fat intake in patients with hyper absorption (increase total cholesterol and LDL-C). Anorexia nervosa (isolated hypercholesterolemia occur as a result of mobilization of cholesterol from tissue). (Goldderg 2008)
Causes follow Hypertriglyceridemia: Cushing’s syndrome (is also associated with hypercholesterolemia). Lipodystrophy and type 1 glycogen storage disease. Consumption of simple carbohydrate including fructose (increase VLDL secretion in some patient), systemic lupus erythematous, and retinoid therapy (also associated with low HDL-C), bile acid sequestrants (can exacerbate hypertriglyceridemia in patient with preexisting triglyceride elevation). (Goldderg 2008)
Causes follow decrease HDL-C: Secondary to hypertriglyceridemia regardless of cause (except alcohol and estrogen-induced hyperlipidemia). Anabolic steroids and probucol (can decrease HDL-C without increasing triglyceride), cigarette smoking, sedentary lifestyle, very low fat diet and MI or a major surgical procedure (can temporarily lower HDL-C). (paul et al., 2000)

Hypolipidemia: Hypolipidemia is a decrease plasma lipoprotein caused by primary (genetic) or secondary factors. It is usually asymptomatic and diagnosed incidentally on routine lipid screening. (Goldderg 2008)

Abetalipoproteinemia: This is autosomal recessive condition caused by mutations in the gene for microtonal triglyceride transfer protein, a protein critical to chylomicron and VLDL (Apo-B) formation. Dietary fat cannot be absorbed and lipoprotein in both metabolic pathways are virtually absent from serum; total cholesterol (TC) is typically less than 45 mg/dl, triglycerides (TGs) are less than 20 mg/dl and LDL are undetectable. (Goldderg 2008)

Hypolipoproteinemia: Is caused by genetic defect leading to absent or decreased LDL and HDL level. Absent LDL and low serum cholesterol lead to a failure to thrive, steatorrhea, central nervous system degeneration, and malabsorption of fats and vitamins. Decrease LDL lead to an increased life expectancy and decreased risk of MI. Reduced HDL lead to an increased risk of atherosclerosis. Absent HDL (tangier disease)lead to an accumulation of cholesterol ester in tonsils, adenoids and spleen. It is considered a benign disease. (hubbard 2010)

1.5 Diagnosis

Dyslipidemia is suspected in patient with characteristic physical findings or complications of dyslipidemia, as an example atherosclerotic disease. Primary lipid disorder is suspected when patient have physical signs of dyslipidemia, onset of premature atherosclerotic disease (at < 60 years), a family history of atherosclerotic disease, or serum cholesterol > 240 mg/dl. Dyslipidemia is diagnosed by measuring serum lipids. Routine measurements of lipid profiles include TC, TGs, HDL-C and LDL-C. Tests for secondary causes of dyslipidemia- including measurements of fasting glucose, liver enzyme, creatinine, and urinary protein- should be done in most patients with newly diagnosed dyslipidemia and when a component of the lipids profile has inexplicably change for the worse. (Goldderg 2008)
Fasting lipid profiles should be obtained in all adults > 20 years and should be repeated every 5 years. Lipids measurements should be accompanied by assessment of other cardiovascular risk factors, defined as: DM, cigarettes use, hypertension and family history of CHD in a male 1st degree relative before age 55 or female 1st degree relatives before age 65. A define age after which patients no longer require screening has not been established, but evidence supports screening of patients into their 80 years, especially in the presence of atherosclerotic cardiovascular disease. Indications of screening patients < 20 years are atherosclerotic risk factors such as DM, hypertension, cigarette smoking and obesity; premature CHD in a parent, grandparent, or sibling; or a cholesterol level > 240 mg/dl or known dyslipidemia in a parent. If information of relatives is unavailable, as in the case of adopted children, screening is at the discretion of the health care practitioner. Patients with an extensive family history of heart disease should also be screened by measuring lipoprotein (a) level. (Goldberg 2008)

1.6 List of psychological disorders
Psychological disorders, also known as mental disorders are patterns of behavioural or symptoms that impact multiple areas of life, these disorder create distress for the person experiencing these symptoms. The following list of psychological disorders includes some of the major categories of psychological disorders listed in the diagnostic and statistical manual of mental disorders as well as several example of each type of psychological disorder (kessler et al., 1994)

Adjustment Disorders This classification of mental disorders is related to an identifiable source of mental stress that causes significant emotional and behavioural symptoms. The diagnostic criteria include:

- Distress that marked and excessive for what would be expected from the stressor.
- Create significant impairment in school or social environment.

In addition to these requirement the symptoms must occur with in three months of exposure to the stressor, the symptoms must not meet the criteria for axis I or axis II disorder the symptoms must not related to bereavement and the symptom must not
last for longer than six months after exposure to stressor. (National institute of mental health 2008)

Anxiety disorder are those that characterized by excessive and abnormal fear, worry and anxiety. Type of Anxiety disorder include; Agoraphobia, Generalized anxiety, Social anxiety disorder, Phobias, Panic disorder, Separation anxiety, and Post traumatic stress disorder. (kessler et al., 1994)

Dissociative disorders are psychological disorder that involve disassociation or Interruption in aspects of consciousness, including identity and memory and that include:

- Dissociative fugue
- Dissociative disorder formerly known as multiple personality disorder
- Dissociative identity disorder
- Depersonalization. [14]

Eating disorders are characterized by obsessive concerns with weight and mental disruptive eating patterns that negatively impact physical and mental health. Types of eating disorder include; Anorexia nervosa, Bulimia nervosa, and Rumination disorder. (kessler et al., 1994)

These psychological disorder are those in which an individual acts as if he or she has an illness, often be deliberately faking or exaggerating symptoms or even self inflicting damage to the body. Types of factitious disorder include; Mnuchausen syndrome by proxy, Ganser syndrome, and Munchausen syndrome. (kessler et al., 1994)

Impulse control disorder are those that involve disorders an ability to control impulse, resulting in harm to one self or others, and include; Kleptomania (stealing), Pyromania (fire-starting), Trichotillomania (hair-pulling), Pathological gambling, Intermittent explosive disorder, and Dermatillomania (skin-picking). (kessler et al., 1994)
Mental disorder due to general medical condition This types of psychological disorder is caused by an under lying medical condition. Medical condition can cause psychological symptom such as citation and personality changes. Example of mental disorders due to general medical condition include; Psychotic disorder due to epilepsy, Aids related psychosis, Depression caused by diabetes, and Personality changes due to brain damage. (kessler et al., 1994)

Neurocognitive disorders These psychological disorders are those that involve cognitive abilities such as memory, problem solving and perception. Some anxiety disorder, mood disorders and psychotic disorders are classified as cognitive disorders. Type of cognitive disorders in; Delirium, Alzheimers, Dementia, and Amnesia. (kessler et al., 1994)

Mood disorder is a term given to a group mental diseases characterized by change in mood, and include; Bipolar disorder, Major depressive disorder, and Cyclothymiacs disorder. (kessler et al., 1994)

Neurodevelopment disorders, Developmental disorders, also referred to as childhood disorders, are those are typically diagnosed during infancy, childhood or adolescence, and these include; Intellectual disability( or intellectual developmental disorder) formerly referred to as mental retardation, communication disorders, Autism, Learning disability, Attention –deticit hyper activity disorders, Conduct disorder, and Oppositional deficient disorder. (kessler et al., 1994)

1.7 Previous Studies

Study conducted in Singapore 2009, found significant increases in serum levels of triglyceride, low-density lipoprotein and total cholesterol (verma et al., 2009) In a study carried out in Finland (1997-1998), found that prevalence of hypercholesterolemia, high LDL cholesterol, and hypertriglycerideridemia was high in persons using antipsychotic medication. (saari et al., 2004)
1.3 Rationale

Cardiovascular disease is the leading cause of deaths worldwide, though, since the 1970s, cardiovascular mortality rates have declined in many high-income countries [17, 18]. At the same time, cardiovascular deaths and disease have increased at a fast rate in low- and middle-income countries.[19] Although cardiovascular disease usually affects older adults, the antecedents of cardiovascular disease, notably atherosclerosis, begin in early life, making primary prevention efforts necessary from childhood [18]. Available data on psychiatric medication (olonzapine, clozapine and phenothiazines ) suggest that it affect in body weight an share the prosperity of increase in serum TGs with modest affect on TC and impact of hyperlipidemia on cardiovascular risk[12]. No published data have been yet found regarding antipsychotic medications in Sudan. In Sudan we need more studies to identify and highlight the effect of antipsychotic medications on lipids profiles in Sudanese psychiatric population. Accordingly the study has been conducted to address the problem.
1.4 Objectives

1.4.1 General Objective

- To evaluate the antipsychotic medications effect on lipid profile in psychiatric men.

1.4.2 Specific Objectives

- To estimate the plasma lipids profile (Cholesterol, Triglycerides, HDL-Cholesterol and LDL-Cholesterol) in study group.
- To compare the result of plasma lipids with psychiatric and non-psychiatric subject.
- To correlate between the duration of medications and plasma lipids of psychiatric subjects.