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Assessment of Serum Gamma Glutamyl Transferase and Albumin levels among Patients with Tuberculosis under Treatments

تقييم انزيم جاما جلاتمايل ترانسفريز والالبيومين في الاشخاص المصابين بالدرن وتحت العلاج

A dissertation submitted inpartial fulfillment for the requirement of M.Sc. degree in Medical Laboratory Science -Clinical chemistry

By:

Adil Ibrahim Awad Abdelmutaal

B.Sc.in Medical Laboratory Sciences - Clinical chemistry

(Omdurman Islamic University -2013)

Supervisor:

Dr.Abdelkarim Abubaker

Associated Professor of Clinical Chemistry

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Dedication

This thesis is dedicated to:

The sake of Allah, my creator and my master. My great teacher and messanger, Mohammed (May Allah bless and grant him), who taught us the purpose of life.

My home land Kassala , the symbol of beauty.

My great parents who never stop giving of themselves in countless ways.

To my father soul.....

My beloved brothers and sisters ; particularly my dearest brother, Osama and sister saida who stand by me when things look bleak. To all my family, the symbol of love and giving.

To my previous viancee, who leads me through the valley of darkness with light of hope and support.

To my future wife.....

All the people in my life who touch my heart.

I dedicated this research.

Acknowledgments

In the name of Allah the most merciful, the most compassionate all praise be to Allah, the lord of the world; and prayers and peace be upon mohammed his servant and messanger.

First and foremost , I must acknowledge my limitless thanks to Allah , the ever magnificent; the ever thankful for his help and bless. I am totally sure that this work would have never become truth without his guidance.

I owe a deep debt of gratitude to Sudan University for Science and Technology for giving us opportunity to complete this work.

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I would like to take this opportunity to say warm thanks to Kassala hospital department of Tuberculosis and special thanks to Rama Specialist Hospital .

Abstract

Tuberculosis still a major problem in Sudan and the anti tuberculosis drugs continue to be problematic in a systemic manner, which affect the liver leads to hepatotoxicity and elevation of liver parameter .

The aim of the study to determine the levels of albumin and GGT in patients with tuberculosis under treatment and compare the level of albumin and GGT according to sex and type of drugs. This study was conducted at Kassala state during April to July 2017. In this study eighty blood samples were tested, sixty samples from known patients with TB under treatment and twenty control samples.

The study demonstrated that albumin was significantly decreased among TB patients under treatment compared to control group (Mean±SD: 2.96±0.48g/dl) for cases and (Mean±SD:4.45±0.59 g/dl) for control group with P.Value 0.000 .

GGT was significantly increased among TB patients under treatment compared with control group (Mean±SD:87.60±39.29IU/L) for cases (Mean±SD:17.00±3.45 IU/L) for control group with P.Value 0.000 . Also the finding of this study showed that albumin was significantly decreased in patients under medication with rifampin compared with control group (Mean ± SD: 3.17± 0.48 g/dl) for cases and (Mean±SD:4.45±0.59 g/dl) for control group with P.Value 0.004. Also albumin show significant decrease in patients under mixed medication with rifampin and ethumbutol compared with control group (Mean±SD:2.73±0.30 g/dl) for cases and (Mean±SD:4.45±0.59 g/dl) for control group with P.Value 0.007.Albumin also show significant decrease in patients under mixed medication with rifampin, ethumbutol and pyrazinamide compared with control group (Mean ± SD:2.81 ±0.45 g/dl) for cases and (Mean ± SD :4.45±0.58 g/dl) for control with P.Value 0.006 .

GGT showed a significant increase in all patients using different (single or mixed) types of TB treatment (RIF, RIF+EMB, RIF+EMB+PZA), P.value (0.004, 0.000, 0.001) respectively.
It is concluded that: using Rifampin and Ethumbutol together for treatment of TB lead to significant changes in albumin and GGT levels.

مستخلص الدراسة

مرض السل الرئوي من الامراض الخطيره وما زال من المشاكل الصحيه كما ان علاج الدرن يؤثر علي وظائف الكبد مما يسبب تلف خلايا الكبد.

أجريت هذه الدراسة بولاية الخرطوم في الفترة بين شهري ابريل ويوليو في العام 2017 وكان هدف هذه الدراسة تحديد مستوي الالبيومين و انزيم الكبد جاما جلاتمايل للمرضي المصابين بمرض السل الرئوي حسب الجنس ونوع العقار ,وفي هذه الدراسة تم فحص ثمانين عينة دم ,ستون منها لاشخاص مصابون بمرض السل الرئوي تحت العلاج وعشرون عينه لاشخاص اصحاء

أظهرت الدراسه ان مستوي الالبيومين ينقص بصوره كبيره بين المرضي المصابين بمرض السل تحت العلاج مقارنه بمجموعه التحكم (2.96±0,48مقابل 4,45 ±0,59ج\دل) وكان الاحتمال الاحصائي للمقارنه 0,000

اظهر انزيم جاما جلاتمايل ترانسفريز زياده كبيره بين المرضي المصابين بمرض السل تحت العلاج مقارنه بمجموعه التحكم (87,60±39,29 مقابل 17,00 ±3,45 وحده\ل) وكان الاحتمال الاحصائي للمقارنه 0,000

كما اظهرت الدراسه ان الالبيومين ينقص في الاشخاص المصابين الذين يستخمون عقار الريفامبين مقارنه مع مجموعه التحكم (3,17±0,48 مقابل 4,45 ±0,59 ج\دل) وكان الاحتمال الاحصائي للمقارنه 0,004 , ايضا ينقص الالبيومين في الاشخاص المصابين مع استخدام المركب العلاجي عقار الريفامبين والاثيمبيتول مع بعض مقارنه مع مجموعه التحكم بنسبه (2,73±0,30 مقابل 4,45 ± 0,59 ج\دل) وكان الاحتمال الاحصائي للمقارنه 0,007 وايضا ينقص الالبيومين عند استخدام المركب العلاجي عقار الريفامبين والاثيمبيتول والبيرزنمايد مقارنه مع مجموعه التحكم بنسبه (2,81±0,45 مقابل 4,45 ±0,59ج\دل) وكان الاحتمال الاحصائي للمقارنه 0,006

اظهر انزيم جاما جلاتمايل زياده عند كل الاشخاص المصابين بالمرض الذين يستخدمون علاجات مختلفه (احادي او مركب) للمرض (الريفامبين, الريفامبين+الاثيمبيتول , الريفامبين+الاثيمبيتول+البيرزنمايد) وكان الاحتمال الاحصائي للمقا(0,004 ,0,000 ,0,001) علي التوالي .

خلصت هذه الدراسه انه عند استخدام الريفامبين والاثيمبيتول مع بعض لعلاج السل الرئوي يؤدي الي تغيرات كبيره في معدل الالبيومين وانزيم جاما جلاتمايل ترانسفريز .

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List of abbreviation

AIDS	Acquired immune deficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate amino transferase
BCG	Bacillus Calmette-Guérin
DNA	Deoxy ribo nucleic acid
EMB	Ethumbutol
GGT	Gamma glutamyltransferase
HIV	Human immune virus
IGRA	Interferon gamma release assay
INH	Isoniazid
KDA	Killo Dalton
LTBI	Latent tuberculosis infection
MDR	Multi drug resistance
MIC	Minimum inhibitory concentration
MTB	Mycobacterium tuberculosis
MTBC	Mycobacterium tuberculosis complex
NTM	Non tuberculousmycobactria
PZA	Pyrazinamide
RIF	Rifampin
RNA	Ribo nucleic acid
TB	Tuberculosis
TNF	Tumor necrosis factor
TST	Tuberculin skin test
WHO	World health organization

1.1.Introduction

Tuberculosis (TB) is one of the most common infectious diseases globally. The World Health Organization (WHO) reports showed that there were an estimated 9.3 million incident cases and 13.7 million prevalent cases of TB in 2007 (WHO, 2009). The WHO declared TB a global health emergency in 1993, and the Stop TB Partnership developed a Global Plan to Stop Tuberculosis that aims to save 14 million lives between 2006 and 2015 (Martin et al, 2016). In 2004, around 14.6 million people had active TB disease with 9 million new cases. The annual incidence rate varies from 356 per 100,000 in Africa to 41 per 100,000 in the Americas (WHO, 2009). The rise in human immune virus (HIV) infections and the neglect of TB control programs have enabled a resurgence of tuberculosis (Migliori, 2009). The emergence of drug-resistant strains has also contributed to this new epidemic TB, from 2000 to 2004, 20% of TB cases being resistant to standard treatments and 2% resistant to second-line drugs (Sobero et al, 2009)The most effective antituberculous (anti-TB) therapy is a combination of isoniazid (INH), rifampin and pyrazinamide (PZA) for 8 weeks, followed by isoniazid and rifampin . Despite the development of this powerful regimen. If serious side-effects do occur and treatment with one of the three drugs must be finally terminated; the patient no longer receives the best treatment available and might be at a higher risk of treatment failure and relapse (Ormerod et al, 1998).A major adverse reaction to one of the first-line antituberculosis drugs, which results in discontinuation of that drug, has several implications. There may be considerable morbidity, even mortality,particularly with drug-induced hepatitis **(**Kopanoff et al , 2002 ; Schaberg, 2009).The occurrence, risk factors, morbidity, and mortality of adverse events from isoniazid (INH), particularly hepatotoxicity have been well defined which effect on liver function mainly liver

enzymes(Kopanoff et al, 2002).However, studies of patients treated for active disease, or receiving 2 months of RIF and PZA for latent infection,have reported serious adverse events attributable to PZA(Daphnee, 2003). Albumin is one of the most important serum proteins produced in the liver. Epidemiological data consistently show that reduced levels of serum albumin, is associated with increased mortality and associated with chronic disease such as TB.HIV.Hepatitis B and C (Junghan et al, 2014).

1.2 Rational:

Tuberculosis is the world's second most common cause of death from infectious disease after acquired immune deficiency syndrome and still a major problem in sudan.

The most frequent adverse effects of anti tuberculosis treatment is hepatotoxicity ,skin reaction ,gastrointestinal and neurological disorder.

Hepatotoxicity is the most serious one which mainly effect the liver and leads to various damage to liver and also can be fetal when not recognized early and when therapy is not interrupted in time.

Albumin evaluation is to detect severity of liver disease (chronic and acute) and to explain whether there was any history of liver disease.

GGT estimation is to detect liver disease or any liver damage as standard clinical estimation of liver dysfunction and it is useful index of suspicion alcoholic among tuberculosis patients.

The measurement of albumin and GGT may be used as biochemical marker for diagnosis of hepatotoxicity in patients with TB under treatments.

1.3 Objectives:

1.3.1 The General objective

To assess the levels of albumin and GGT among patients with tuberculosis under treatment in kassala state .

1.3.2 Specific objectives:

1. To evaluate the level of liver enzyme GGT in patients with TB under treatment(Isoniazid,Rifampin,Ethumbutol and Pyrazinzmide) for at least two months and control group.
2. To measure albumin in patients with TB under treatment (Isoniazid,Rifampin,Ethumbutol and Pyrazinzmide) for at least two months and control group.
3. To estimate the change in albumin and GGT level according to gender.

2. Literature Review

2.1 Tuberculosis

Tuberculosis is an infectious disease caused by mycobacterium tuberculosis(MTB)· Tuberculosis generally affects the lungs, but can also affect other parts of the body. Most infections do not have symptoms, in which case it is known as latent tuberculosis. About 10% of latent infections progress to active disease which, if left untreated, kills about half of those infected. The classic symptoms of active TB are a chronic cough with blood-containingsputum, fever, night sweats, and weight loss The historical term "consumption" came about due to the weight loss ·Infection of other organs can cause a wide range of symptoms (Dolin et al, 2010). Tuberculosis spread through the air when people who have active TB in their lungs cough, spit, speak, or sneeze. People with latent TB do not spread the disease. Active infection occurs more often in people with HIV/AIDS and in those who smoke. Diagnosis of active TB is based on chest X-rays, as well as microscopic examination and culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) or blood tests (Konstantinos , 2010) . Prevention of TB involves screening those at high risk, early detection and treatment of cases, and vaccination with the Bacillus Calmette-Guérin vaccine. Those at high risk include household, workplace, and social contacts of people with active TB. Treatment requires the use of multiple antibiotics over a long period of time. Antibiotic resistance is a growing problem with increasing rates of multiple drug-resistant tuberculosis (MDR-TB). (Hawn et al, 2014)

One-third of the world's population is thought to be infected with TB. New infections occur in about 1% of the population each year. In 2014, there were 9.6 million cases of active TB which resulted in 1.5 million

deaths. More than 95% of deaths occurred in developing countries. The number of new cases each year has decreased since 2000. About 80% of people in many Asian and African countries test positive while 5–10% of people in the United States population tests positive by the tuberculin test. Tuberculosis has been present in humans since ancient times(Kumar et al, 2007)

2.1.1 Signs and symptoms

The main symptoms of variants and stages of tuberculosis are given, with many symptoms overlapping with other variants, while others are more (but not entirely) specific for certain variants. Multiple variants may be present simultaneously.Tuberculosis may infect any part of the body, but most commonly occurs in the lungs (known as pulmonary tuberculosis). Extrapulmonary TB occurs when tuberculosis develops outside of the lungs, although extrapulmonary TB may coexist with pulmonary TB (Dolin et al, 2010). General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue. Significant nail clubbing may also occur (Gibson et al, 2005).

2.1.2 Causes

The main cause of TB is mycobacterium tuberculosis (MTB), a small, aerobic, nonmotilebacillus. The high lipid content of this pathogen accounts for many of its unique clinical characteristics. It divides every 16 to 20 hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour. Mycobacteria have an outer membrane lipid bilayer If a Gram stain is performed, MTB either stains very weakly "Gram-positive" or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall. MTB can

withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of ahost organism, butM.tuberculosis can be cultured in the laboratory.(Southwick 2007)

2.1.3 Risk factors

Risk factors for tuberculosis

A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all people with TB are infected by the virus. This is a particular problem in sub-Saharan Africa, where rates of HIV are high. Of people without HIV who are infected with tuberculosis, about 5–10% develop active disease during their lifetimes; in contrast, 30% of those co-infected with HIV develop the active disease.(Chaisson et al, 2008). Chronic lung disease is another significant risk factor. Silicosis increases the risk about 30-fold. Those who smoke cigarettes have nearly twice the risk of TB compared to nonsmokers. Other disease states can also increase the risk of developing tuberculosis. These include alcoholismand diabetes mellitus (three-fold increase). Certain medications, such as corticosteroids and infliximab (an anti-αTNF monoclonal antibody), are becoming increasingly important risk factors, especially in the developed world. Genetic susceptibility also exists, for which the overall importance remains undefined.(Vanzylsmit , 2010)

2.1.4 Mechanism of Transmission

When people with active pulmonary TB cough, sneeze, speak, sing, or spit, they expel infectious aerosol droplets 0.5 to 5.0 μm in diameter. A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease, since the infectious dose of

tuberculosis is very small (the inhalation of fewer than 10 bacteria may cause an infection).People with prolonged, frequent, or close contact with people with TB are at particularly high risk of becoming infected, with an estimated 22% infection rate. A person with active but untreated tuberculosis may infect 10–15 (or more) other people per year.Transmission should occur from only people with active TB – those with latent infection are not thought to be contagious.(Cole et al, 1998)

2.1.5 Diagnosis

Diagnosis of active tuberculosis based only on signs and symptoms is difficult, as is diagnosing the disease in those who are immune suppressed. A diagnosis of TB should, however, be considered in those with signs of lung disease or constitutional symptoms lasting longer than two weeks. A chest X-ray and multiple sputum cultures for acid-fast bacilli are typically part of the initial evaluation. Interferon-γ release assays and tuberculin skin tests are of little use in the developing world. Interferon gamma release assays (IGRA) have similar limitations in those with HIV.(Escalante, 2009).

2.1.6 Epidemiology

Tuberculosis is the second-most common cause of death from infectious disease (after those due to HIV/AIDS). The total number of tuberculosis cases has been decreasing since 2005, while new cases have decreased since 2002. China has achieved particularly dramatic progress, with about an 80% reduction in its TB mortality rate between 1990 and 2010. The number of new cases has declined by 17% between 2004 and 2014. Tuberculosis is more common in developing countries; about 80% of the

population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the US population test positive. Hopes of totally controlling the disease have been dramatically dampened because of a number of factors, including the difficulty of developing an effective vaccine, the expensive and time-consuming diagnostic process, the necessity of many months of treatment, the increase in HIV-associated tuberculosis, and the emergence of drug-resistant cases in the 1980s.(Lozano et al, 2012)

In 2007, the country with the highest estimated incidence rate of TB was Swaziland, with 1,200 cases per 100,000 people. India had the largest total incidence, with an estimated 2.0 million new cases. In developed countries, tuberculosis is less common and is found mainly in urban areas. Rates per 100,000 people in different areas of the world were: globally 178, Africa 332, the Americas 36, Eastern Mediterranean 173, Europe 63, Southeast Asia 278, and Western Pacific 139 in 2010. In Canada and Australia, tuberculosis is many times more common among the aboriginal peoples, especially in remote areas. In the United States Native Americans have a fivefold greater mortality from TB, and racial and ethnic minorities accounted for 84% of all reported TB cases.(Anee 2009) Incidence of tuberculosis in sudan was reported in 2015 total cases was 19 thousand according to the world bank collection of development indicators compiled from officially recognized sources.

2.2 Tuberculosis drugs

2.2.1 Isoniazid

is one of the most important drugsin the treatment of tuberculosis. It has been used since 1952. The structure of isoniazid is simple. Itcomprises a pyridine ring and a hydrazine group.The minimum inhibitory

concentration (MIC) of isoniazid for Mycobacterium tuberculosisis 0.02-0.20 μg/mL. Although isoniazid has abactericidal effect on rapidly growing bacilli, ithas a limited effect on slow-growing (generally intracellular) and intermittently growing (generally extracellular) bacilli.daily dose is 5mg/kg ,maximum 300mg**.(** Zhang , 2005)

2.2.1.1 Minor adverse effects

• Nausea, vomiting, and epigastric pain:Taking the drug 2 h after the first meal and using symptomatic medication (metoclopramide, ranitidine, or omeprazole) can relieve the symptoms.

• Transitory and asymptomatic increase inhepatic enzyme levels.

• Arthralgia: Arthralgia is a rare complication of isoniazid administration and respondsto treatment with non steroidalanti-inflammatory drugs.

• Changes in behavior: Headache, insomnia,euphoria, agitation, anxiety, andsomnolence can occur in patients receiving isoniazid.

• Acne: Acne on the face and torso is acommon manifestation that disappears when isoniazid is discontinued.

• Cutaneous pruritus or fever: Patients report developing cutaneous pruritus or fever after taking isoniazid.(Silva, 2004)

2.2.1.2 Major adverse effects

• Psychosis, convulsive seizures, mental confusion, and coma: In patients receiving isoniazid, neurological and psychiatric manifestations are less common, more severe, and often difficult to diagnose.

• Hematological alterations or vasculitis:Hematological alterations and vasculitisare rare complications of isoniazid administration and occur due to hypersensitivity.

• Peripheral neuropathy: Peripheral neuro pathyoccurs in approximately 20% ofpatients treated with isoniazid. It is dose dependent and

uncommon at a dose of5 mg • kg−1 • day−1. It is more commonat doses higher than 300 mg/day.

• Clinical hepatitis: Recent studies have shown that the incidence of clinical hepatitis in patients receiving isoniazid islower than previously thought.

Isoniazid is a hepatotoxic drug, the effect which becomes more evident in individuals with liver disease, in alcoholic individuals, and in individuals over 50 years of age. In such patients,the half-life of isoniazid is longer, and the serumlevels of the drug are higher. These patients should be closely monitored and should undergo clinical examination and laboratory tests morefrequently than is necessary for patients without liver disease.(Thwaites et al, 2009)

2.2.2 Rifampin

Rifampin is the most important drug in the treatment of tuberculosis. The drug has been used since 1966 and the MIC of rifampin for M. tuberculosis is 0.05-0.50 μg/mL.Rifampin is a bactericidal drug that kills growing,metabolically active bacilli, as well as bacilli inthe stationary phase, during which metabolism isreduced. When rifampin is used in combination with pyrazinamide, tuberculosis treatment duration can be reduced to six months. Daily dose is 10mg/kg ,maximum 600mg.(Zhang 2005)

2.2.2.1 Minor adverse effects

• Gastrointestinal reactions: Nausea,anorexia, and abdominal pain can occurin patients treated with rifampin.

• Orange-colored tears, sweat, and urine:Patients should be alerted to the possibility that rifampin administration can cause discoloration of body fluids. Orange colored tears can stain contact lenses.

• Skin reaction: Pruritus, with or without erythema, occurs in 6% of patients receiving rifampin.

• Flu-like syndrome: Flu-like syndrome is rare and occurs in patients who use intermittent regimens that include rifampin.

• Fatigue, dizziness, headache, dyspnea, andataxia can also occur in patients treated with rifampin.(Sun et al, 2009)

2.2.2.2 Major adverse effects

• Exanthema: Exanthema can occur due tothe use of rifampin or of another drug administered in combination with rifampin.If exanthema occurs, treatment should be discontinued, and the drugs should be subsequently reintroduced, one by one, inorder to identify the causative drug.

• Hepatotoxicity: Transitory and asymptomatic increases in the serum levels ofbilirubin and hepatic enzymes occur in 5%of patients treated with rifampin. Thoselevels subsequently normalize, without the need to discontinue the treatment.However, cholestatic hepatitis occurs in 2.7% of the patients receiving rifampinin combination with isoniazid and in upto 1.1% of those receiving rifampin in combination with antituberculosis drugs other than isoniazid.

• Immunological reactions: Thrombocytopenia,leukopenia, eosinophilia, hemolytic anemia, agranulocytosis, vasculitis, acuteinterstitial nephritis, and septic shock can occur after rifampin administration.(Sun et al, 2009)

2.2.3 Pyrazinamide

Pyrazinamide is a nicotinic acid derivative,the molecular structure of which is similar tothat of isoniazid. However, there is no cross resistance of M. tuberculosis to pyrazinamide and isoniazid. Pyrazinamide was synthesized in1936 and has been used as an antituberculosis drug since 1952. The MIC of pyrazinamide for M.tuberculosis is 6.25-50.0 μg/mL at

a pH of5.5. After oral administration, pyrazinamide iswell absorbed and widely distributed throughout the body. The plasma concentration of thedrug peaks within 2 h after its administration.Pyrazinamide is bactericidal and has a potent sterilizing effect, principally in the acid medium within macrophages and at sites of acute inflammation. In patients with tuberculosis induced lung injury and growth of the bacilli. those are phagocytosed by macrophages are inhibited by the acid environment within the phagolysosomes. Growth is also inhibited in the inflammatory zones of the cavitary wall due to the acid pH in those zones. Pyrazinamide is the most effective drug in eliminating this population.M. tuberculosisisthe only microorganism that is susceptible to pyrazinamide .Daily dose is 20-25mg/kg ,maximum 2000mg .(Zhang , 2009)

2.2.3.1 Minor adverse effects

• Gastrointestinal symptoms: Nausea,vomiting, and anorexia are common in patients treated with pyrazinamide.

• Hyperuricemia and arthralgia in non-gouty individuals: In non-gouty patients receiving pyrazinamide, hyperuricemia commonly leads to arthralgia.The mechanism is related to pyrazinoic acid, the principal metabolite of pyrazinamide, which inhibits the renal tubular secretion of uric acid.This rarely requires that pyrazinamide be discontinued or that the dose beadjusted. The hyperuricemia is typically asymptomatic, and the pain responds wellto treatment with aspirin or non steroidal anti-inflammatory drugs.

• Exanthema and pruritus: Exanthema andpruritus are relatively common effects of pyrazinamide administration. In most cases,these improve with the administration of anti histamines.

• Dermatitis: Treatment with pyrazinamide can cause photosensitivity dermatitis.(Blumberg et al, 2003)

2.2.3.2 Major adverse effects

• Severe exanthema and pruritus: Ifsevere exanthema and pruritus occur,pyrazinamide should be discontinued.

• Rhabdomyolysis with myoglobinuria and kidney failure.

• Acute arthritis in gouty individuals: In patients receiving pyrazinamide.

• Hepatotoxicity: Pyrazinamide is the most hepatotoxic of the drugs cited in the present study. Therefore, it is essential that the doses of the drug be adjusted to the weight of the patient. Liver impairment is rare if the drug is administered at amaximum dose .(Blumberg et al, 2003)

2.2.4 Ethambutol

Ethambutol was synthesized in 1961 and has been used in the treatment of tuberculosis since1966. It acts on intracellular and extra cellular bacilli, principally on rapidly growing bacilli.The MIC of ethambutol for M. tuberculosis is 1-5 μg/mL. At the usual doses, ethambutol has a bacteriostatic effect. Daily dose is 15-20mg/kg ,maximum 1600mg.
Symptoms (nausea,vomiting, abdominal pain, and hepatotoxicity).(Zhang , 2009)

2.2.5 Streptomycin

Streptomycin is an aminoglycoside antibiotic derived from streptomyces griseus that is used in the treatment of TB and sensitive Gram-negative infections.

Streptomycin is not absorbed from the gastrointestinal tract but, after intramuscular administration, it diffuses readily into the extracellular component of most body tissues and attains bactericidal concentrations, particularly in tuberculous cavities. Little normally enters the cerebrospinal fluid, although penetration increases when the meninges are inflamed. The plasma half-life, which is normally 2–3 hours, is considerably extended in the newborn, the elderly and patients with severe renal impairment. Streptomycin is excreted unchanged in the urine.(American Thoracic Society, 2003)

2.2.5.1 Adverse effects

Streptomycin injections are painful. Rash, induration, or sterile abscesses can form at injection sites.

Numbness and tingling around the mouth occur immediately after injection.

Cutaneous hypersensitivity reactions can occur.

Impairment of vestibular function is uncommon with currently recommended doses. Hearing loss is less common than vertigo. Manifestations of damage to the 8th cranial (auditory) nerve include ringing in the ears, ataxia, vertigo and deafness; damage usually occurs in the first 2 months of treatment and is reversible if the dosage is reduced or the drug is stopped .

Streptomycin is less nephrotoxic than other aminoglycoside antibiotics. If urinary output falls, albuminuria occurs or tubular casts are detected in the urine, streptomycin should be stopped and renal function should be evaluated.Haemolyticanaemia, aplastic anaemia, agranulocytosis, thrombocytopenia and lupoid reactions are rare adverse effects.

Adults: 15 mg/kg (12–18 mg/kg) daily, or 2 or 3 times weekly; maximum daily dose is 1000 mg.The use of fixed-dose combination capsules or tablets facilitates DOT administration by minimizing the chance for error through the use of fewer tablets and may reduce the risk of acquired drug resistance since one medication cannot be selectively taken.Hepatic Toxicity.(Toman 2004)

Liver injury can be caused by three of the first-line TB disease drugs, INH, RIF and PZA. Significant liver toxicity is indicated by AST ≥3 times the upper limit of normal in the presence of symptoms, or ≥5 times the upper limit of normal in the absence of symptoms . If the AST and

ALT are <5 times the upper limit of normal, toxicity can be considered mild; an AST or ALT of 5– 10 times normal defines moderate toxicity; and >10 times normal is severe. In addition to elevation of the AST and ALT, occasionally there are disproportionate increases in bilirubin,GGT and alkaline phosphatase. This pattern is more consistent with RIF hepatotoxicity .(American Thoracic Society2003)

2.3 The Liver

Liver is the large metabolically active organ involve in homeostasis and detoxification, it is an important multifunctional organ with major role in the synthesis of plasma protein, detoxification and excretion of exogenous and endogenous potentially toxic substance, and in digestion and absorption through the secretion of bile (David 2008).

2.3.1 Detoxification and Drug Metabolism:

Hepatocytes have the ability to metabolize, detoxification and inactivated exogenous compounds such as drugs and insecticides and as steroid.

The liver is serving to protect the body from the injurious substance absorbed from the intestinal tract and toxic products of metabolism. The most important mechanism in this detoxification activity is the microsomal drug metabolizing system of the liver. This system induced by the many types of drugs and foreign compounds and is responsible for many detoxification mechanisms; include oxidation, reduction, hydrolysis, hydroxylation, carboxylation and demethylation. These mechanisms convert the toxic and other insoluble compounds into other forms or more soluble compounds to be excreted by the kidney (Bishob 2004).

2.4 Albumin:

It is the most abundant protein in human blood plasma; it constitutes about half of serum protein. It is produced in the liver. It is soluble and monomeric.

Albumin transports hormones, fatty acids, and other compounds, buffers pH, and maintains oncotic pressure, among other functions.

Albumin is synthesized in the liver as preproalbumin, which has an N-terminal peptide that is removed before the nascent protein is released from the rough endoplasmic reticulum. The product, proalbumin, is in turn cleaved in the Golgi vesicles to produce the secreted albumin.

The reference range for albumin concentrations in serum is approximately 35 - 50 g/L (3.5 - 5.0 g/dL). It has a serum half-life of approximately 20 days. It has a molecular mass of 66.5 kDa.

The gene for albumin is located on chromosome 4 and mutations in this gene can result in anomalous proteins. The human albumin gene is 16,961 nucleotides long from the putative 'cap' site to the first poly(A) addition site. It is split into 15 exons that are symmetrically placed within the 3 domains thought to have arisen by triplication of a single primordial domain.

2.4.1 Synthesis

Albumin is synthesized in the liver as preproalbumin which has an N-terminal peptide that is removed before the nascent protein is released from t

he rough endoplasmic reticulum. The product, proalbumin, is in turn cleaved in the Golgi vesicles to produce the secreted albumin.(Walker et al, 1990)

2.4.2 Functions of albumin

Maintains oncotic pressure.

Transports thyroid hormones.

Transports other hormones, in particular, ones that are fat-soluble.

Transports fatty acids ("free" fatty acids) to the liver and to myocytes for utilization of energy.

Transports unconjugated bilirubin.

Transports many drugs; serum albumin levels can affect the half life of drugs.

Competitively binds calcium ions (Ca^{2+}).

Serum albumin, as a negative acute-phase protein, is down-regulated in inflammatory states. As such, it is not a valid marker of nutritional status; rather, it is a marker of an inflammatory state.

Prevents photodegradation of folic acid.(Masaki et al, 2006)

2.4.3 Measurement

Serum albumin is commonly measured by recording the change in absorbance upon binding to a dye such as bromocresol green or bromocresol purple.(Masaki et al, 2006)

2.4.4 Reference ranges

Serum albumin concentration is typically 35 - 50 g/L (3.5 - 5.0 g/dL)

2.4.5 Pathology

2.4.5.1 Hypoalbuminemia

Hypoalbuminemia is a low blood albumin levels. This can be caused by:

Liver disease .

Excess loss in bowel (protein-losing enteropathy, e.g., Ménétrier's disease).

Burns (plasma loss in the absence of skin barrier).

Redistribution (hemodilution [as in pregnancy], increased vascular permeability or decreased lymphatic clearance).

Acute disease states (referred to as a negative acute-phase protein).

Malnutrition and wasting.

Mutation causing analbuminemia (very rare).

2.4.5.2 Hyperalbuminemia

Hyperalbuminemia is an increased concentration of albumin in the blood. Typically, this condition is due to abrupt dehydration.

Chronic dehydration needs to be treated with zinc as well as with water·Zinc reduces cell swelling caused by decreased intake of water (hypotonicity) and also increases retention of salt. In the dehydrated

state, the body has too high an osmolarity and, it appears, discards zinc to prevent this. Zinc also regulates transport of the cellular osmolyte to urine, and albumin is known to increase cellular to urine absorption. Zinc has been shown to increase retinol (vitamin A) production from beta-carotene, and in lab experiments retinol reduced human albumin production. It is possible that a retinol (vitamin A) deficiency alone could cause albumin levels to become raised. Patients recovering from chronic dehydration may develop dry eyes as the body uses up its vitamin A store. Retinol causes cells to swell with water (this is most likely one reason that too much vitamin A is toxic). Hyperalbuminemia is also associated with high protein diets.(Mutlui et al, 2006)

2.5 Gamma-glutamyl transferase:

Gamma-glutamyltransferase (GGT) is primarily present in kidney, liver, and pancreatic cells. Small amounts are present in other tissues. Even though renal tissue has the highest level of GGT, the enzyme present in the serum appears to originate primarily from the hepatobiliary system, and GGT activity is elevated in any and all forms of liver disease. It is highest in cases of intra- or post-hepatic biliary obstruction, reaching levels some 5 to 30 times normal. It is more sensitive than alkaline phosphatase (ALP), leucine amino peptidase, aspartate transaminase, and alanine aminotransferase in detecting obstructive jaundice, cholangitis and cholecystitis; its rise occurs earlier than with these other enzymes and persists longer. Only modest elevations (2-5 times normal) occur in infectious hepatitis, and in this condition GGT determinations are less useful diagnostically than are measurements of the transaminases. High elevations of GGT are also observed in patients with either primary or secondary (metastatic) neoplasms. Elevated levels of GGT are noted not

only in the sera of patients with alcoholic cirrhosis but also in the majority of sera from persons who are heavy drinkers. Studies have emphasized the value of serum GGT levels in detecting alcohol-induced liver disease. Elevated serum values are also seen in patients receiving drugs such as phenytoin and phenobarbital, and this is thought to reflect induction of new enzyme activity

Is a transferase (a type of enzyme) that catalyzes the transfer of gamma-glutamyl functional groups from molecules such as glutathione to an acceptor that may be an amino acid, a peptide or water (forming glutamate). Gamma Glutamyl Transferase plays a key role in the gamma-glutamyl cycle, a pathway for the synthesis and degradation of glutathione and drug and xenobiotic detoxification. Other lines of evidence indicate that GGT can also exert a pro-oxidant role, with regulatory effects at various levels in cellular signal transduction and cellular pathophysiology.This transferase is found in many tissues, the most notable one being the liver, and has significance in medicine as a diagnostic marker.(Dominici et al, 2005)

2.5.1 Function of Gamma Glutamyl Transferase

GGT is present in the cell membranes of many tissues, including the kidneys, bile duct, pancreas, gallbladder, spleen, heart, brain, and seminal vesicles. It is involved in the transfer of amino acids across the cellular membrane and leukotriene metabolism. It is also involved in glutathione metabolism by transferring the glutamyl moiety to a variety of acceptor molecules including water, certain L-amino acids, and peptides, leaving the cysteine product to preserve intracellular homeostasis of oxidative stress. This general reaction is:

(5-L-glutamyl)-peptide + an amino acid peptide + 5-L-glutamyl amino acid .(Yokoyama, 2007)

2.5.2 Structure

In prokaryotes and eukaryotes, it is an enzyme that consists of two polypeptide chains, a heavy and a light subunit, processed from a single chain precursor by an autocatalytic cleavage. The active site of GGT is known to be located in the light subunit.

2.5.3 Medical applications

Gamma Glutamyl Transferase is predominantly used as a diagnostic marker for liver disease. Latent elevations in GGT are typically seen in patients with chronic viral hepatitis infections often taking 12 months or more to present. Elevated serum GGT activity can be found in diseases of the liver, biliary system, and pancreas. In this respect, it is similar to alkaline phosphatase (ALP) in detecting disease of the biliary tract. Indeed, the two markers correlate well, though there are conflicting data about whether GGT has better sensitivity. In general, ALP is still the first test for biliary disease. The main value of GGT over ALP is in verifying that ALP elevations are, in fact, due to biliary disease; ALP can also be increased in certain bone diseases, but GGT is not. More recently, slightly elevated serum GGT has also been found to correlate with cardiovascular diseases and is under active investigation as a cardiovascular risk marker. GGT in fact accumulates in atherosclerotic plaques, suggesting a potential role in pathogenesis of cardiovascular diseases, and circulates in blood in the form of distinct protein aggregates, some of which appear to be related to specific pathologies such as metabolic syndrome, alcohol

addiction and chronic liver disease. High body mass index is associated with type 2 diabetes only in persons with high serum GGT.

GGT is elevated by ingestion of large quantities of alcohol. However, determination of high levels of total serum GGT activity is not specific to alcohol intoxication, and the measurement of selected serum forms of the enzyme offer more specific information. Isolated elevation or disproportionate elevation compared to other liver enzymes (such as ALP or alanine transaminase) can indicate alcohol abuse or alcoholic liver disease, and can indicate excess alcohol consumption up to 3 or 4 weeks prior to the test. The mechanism for this elevation is unclear. Alcohol might increase GGT production by inducing hepatic microsomal production, or it might cause the leakage of GGT from hepatocytes. Numerous drugs can raise GGT levels, including barbiturates and phenytoin. GGT elevation has also been occasionally reported following non steroidal anti-inflammatory drugs (including aspirin), St. John's wort and kava. Elevated levels of GGT can also be due to congestive heart failure.

Individual test results should always be interpreted using the reference range from the laboratory that performed the test, though example reference ranges are 15-85 IU/L for men, and 5-55 IU/L for women.(Ruttmann et al, 2005)

3.Materials and Methods

3.1 Materials

3.1.1-Study approach

A quantitative method was used to evaluate albumin and gamma glutamyl transferase levels among patients with tuberculosis under treatment from April to July 2017.

3.1.2-Study design and Study area

This cross sectional (case control) study was conducted in Kassala state- Sudan.

3.1.3- Study populationand Sample size

Patients who came to tuberculosis centre and diagnosed as tuberculosis patients (diagnosed according to chest x ray and sputum smear) and under treatment for at least two months were be recruited as cases and those without disease as control group was enrolled.

Sixety samples were takan from patients with tuberculosis under treatment and twenty samples as healthy control group .

3.1.4-Inclusion criteria

This study include patients with pulmonary tuberculosis disease under treatment for at least two months as well as appearantely healthy as control (match age and gender).

3.1.5-Exclusion criteria

The criteria of exclusion based on excluding any patients with TB who do not use tuberculosis drug , also we excluded new discovery cases and patients who have liver disease .

3.1.6-Ethical consedration

The study was revised and ethically approved by the ethical committee of the Faculty of Medical Laboratory sciences, Sudan Unversity for Science and Technology .Consent was taken regarding acceptance to participate in the study

and re-assurance of confidentialty. Before the specimen was collected, the donors knew that this specimen was collected for research purpose.

3.1.7-Data collection

Data were collected using a structural interviewing questionnaire, which was designed to collect and maintain all valuable information concerning each case examined.

3.1.8-Sample collection and processing

About 2.5 ml of venous blood were collected from each participant (both case and control).An informed consent was taken from all participiant. The sample collected under aseptic conditions and placed in sterile lithium heparin containers and centrifuged for 5 minutes at 3000 RPM to obtain plasma then sample were kept in plain containers at -70C^0 until the time of analysis.

3.2 Methods

3.2.1 Estimation of albumin

3.2.1.1 General principle

Albumin in presence of bromocresol green at slightly acid ph produces a colour change of the indicator from yellow-green to green-blue . The intensity of colour formed is proportional to the albumin concentration in the sample (Gendeler ,1984)

3.2.1.2 Reagents

- Bromocresol green 0.12 mmol/l ph 4.2
- Albumin agueous primary standard 5 g/dl

3.2.1.3 Procedure of albumin measurement(appendiex II)

3.2.2 Estimation of Gamma glutamyltransferase

3.2.2.1 General principle

Gamma glutamyltransferase catalyze the transfer of gamma glutamyl group from gamma glutamyl-3-carboxy-4-nitroanilide to glycyglycine ,librating 3-carboxy-4-

nitroaniline .The catalytic concentration is determined from the rate of 3-carboxy-4-nitroaniline formation .(Beleta, 1990).

3.2.2.2 Reagents

Glycyglycine 206.25 mmol/l , Sodium hydroxide 130 mmol/l , ph 7.9 .

Gamma glutamyl-3-carboxy-4-nitroanilide 32.5 mmol/l .

3.2.2.3 Procedure of GGT measurements (appendix III)-

3.2.3 Quality Control

Quality control specimens werer run with each calibration curve to verify assay performance. To assure proper performance, a statistically significant number of controls were assayed to establish mean values and acceptable ranges.

3.2.4 Statistical analysis

Data was analyzed using statistical package for social science (SPSS) computer Programmed version 21.The results expressed as mean,standard deviation and percentage ,independent T.test was using to compare the quantitive variables. Person correlation was done to study the relation between variables and parametrs. P,value≤0.05 consider as significant.

4.Results

The biochemical results of albumin and GGT in patients with tuberculosis under treatment are given in tables and figures:

Figure(4-1): Gender distrubuation among Tuberculosis patients. Mean age 35 ± 13 Range from 17—98 years.

Table(4-1): Illustrate the mean concentration of albumin and GGT level among cases and controls .Albumin was significantly decrease among TB patients under treatment compared with control group (Mean±SD: 2.96±0.48) g/dl for cases and (Mean±SD:4.45±0.59) g/dl for control group respectively with P.Value 0.000 .

GGT was significantly increase among TB patients under treatment compared with control group (Mean±SD:87.60±39.29) IU/L for cases (Mean±SD:17.00±3.45) IU/L for control group with P.Value 0.000 .

Table(4-2): Illustrate mean concentration of albumin and GGT levels according to type of drug.Albumin show significant decrease with patients under treatment with rifampin (Mean±SD:3.17±0.48) with P.Value 0.004.Also albumin show significant decrease with patients under treatment with mixed drugs (RIF+EMB) (Mean±SD:2.73±0.30) with P.Value 0.007. Albumin also show significant decrease with patients under treatment with mixed dru(RIF+PZA+EMB) (Mean±SD:2.81±0.45) compared to control group (Mean±SD:4.45±0.59) g/dl with P.Value 0.006. the effect of mixed drugs cause a significant changes than using one drug alone.

Patients under treatment with rifampin show significant increase to GGT (Mean ± SD: 66.96±11.2) with P.Value 0.004.Also patients under treatment with mixed drugs (RIF+EMB) show significant increase to GGT(Mean±SD:115.63±47.9) with P.Value 0.000. patients under treatment with mixed drugs (RIF+PZA+EMB) show significant increase to GGT (Mean±SD:100.42±45.1) compared with control group (Mean±SD:17.00±3.45) IU/L with P.Value 0.001.

Table(4-3): Illustrate mean concentration of albumin and GGT across gender distrubuation. Albumin show insignificant difference among male

(Mean±SD:2.91±0.43),and female (Mean±SD:3.05±0.57) with P.Value 0.296 .

GGT show significant increase among male (Mean±SD: 91.94±36.17) ,and female (Mean±SD: 79.52±19.95) with P.Value 0.004 .

Figure(4-2): Show changes in mean of albumin level according to type of drug,for group one the mean was 3.17, group two the mean was 2.73 and for group three was 2.81.

Figure(4-3): Show changes in GGT level mean according to type of drug,for group one the mean was 66.96, group two the mean was 115.63 and for group three was 100.42.

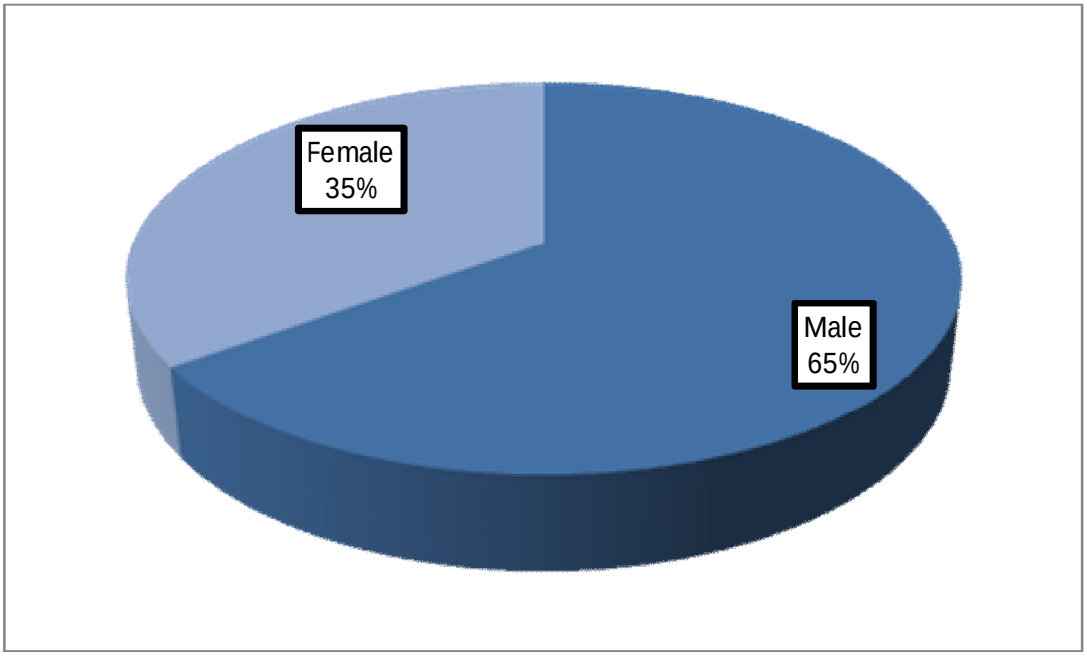


Figure (4-1): Gender distrubuation among TB patients

Mean age 35 ± 13 Range from 17—98 years

Table (4-1): Mean concentration of albumin and GGT among cases and control.

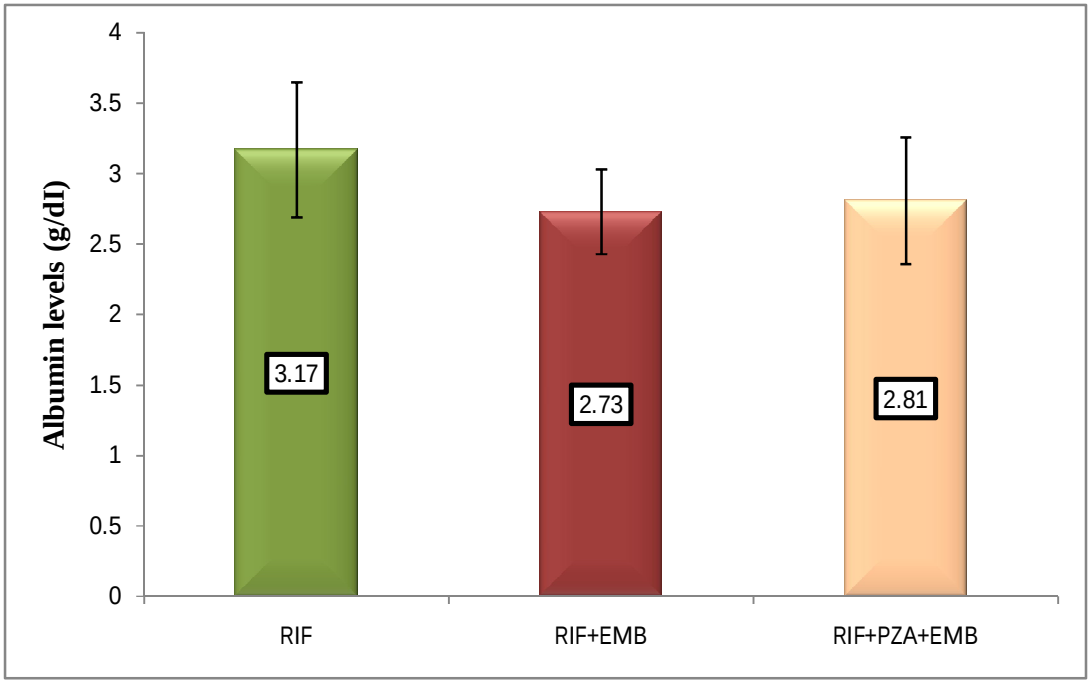
Parameters	Case (Mean±SD)	Control (Mean±SD)	P-value
Albumin (g/dI)	2.96±0.48	4.45±0.59	0.000
GGT(IU/I)	87.60±39.29	17.00±3.45	0.000

Table (4-2): Mean concentration of albumin and GGT levels according to type of drug.

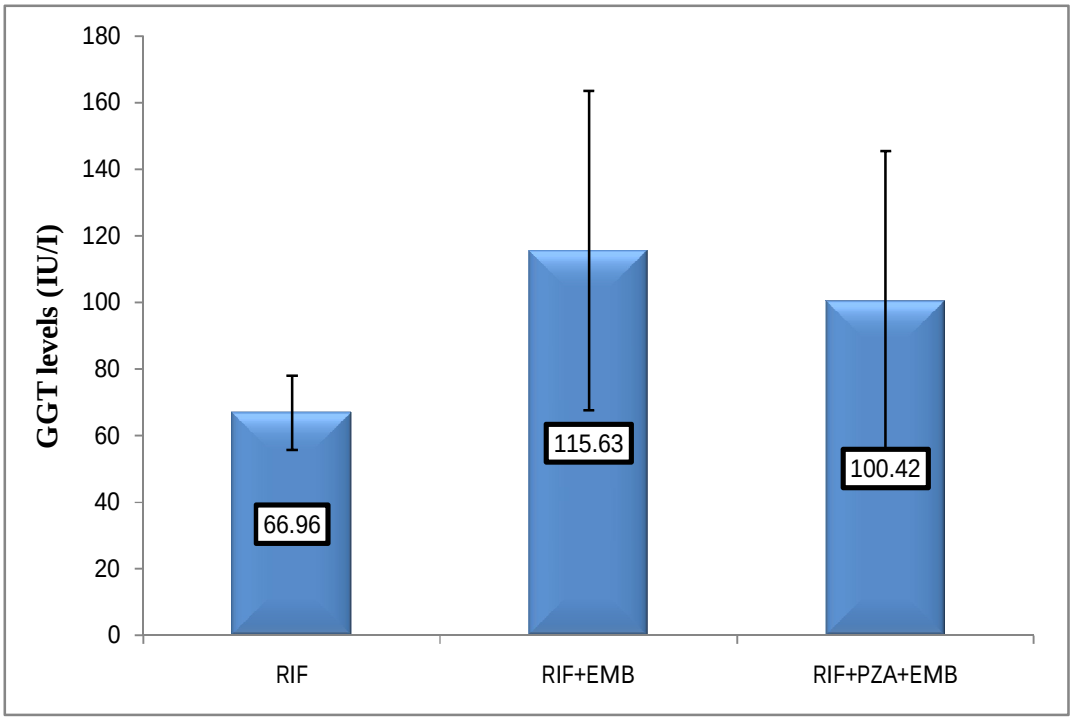
Variables	Type of drugs used in TB patients	Mean±SD	*P-value*
Albumin (g/dI)	Rifampin	3.17±0.48	0.004
	RIF, EMB	2.73±0.30	0.007
	RIF, PZA, EMB	2.81±0.45	0.006
GGT(IU/I)	Rifampin	66.96±11.2	0.004
	RIF, EMB	115.63±47.9	0.000
	RIF, PZA, EMB	100.42±45.1	0.001

Table(4-3): Mean concentration of albumin and GGT across gender distrubuation

Parameters	Male (Mean±SD) No=52	Female (Mean±SD) No=28	P-value
Albumin (g/dI)	2.91±0.43	3.05±0.57	0.296
GGT(IU/I)	91.94±36.17	79.52±19.95	0.004



Figure(4-2): Show changes in albumin level according to type of drugs.



Figure(4-3): Show changes in GGT level according to type of drugs.

5.Discussion

Tuberculosis still a major problem in Sudan and the anti tuberculosis drugs continue to be problematic in a systemic manner, which affect the level of liver's parameters lead to hepatotoxicity .

In this study, the average age of patients from (17 to 98 years).

Estimation of albumin and GGT is to evaluate liver damage as result to anti tuberculosis treatment . Find that albumin mainly decrease in patients with TB under treatment ,these results were in agreement with another study (Salma et al, 2015) which showed insignificant decrease in albumin level among cases 3.06 . (Ahmed et al, 2011) Mean plasma concentration of total plasma protein and plasma albumin were significantly decreased.

Albumin is a negative acute phase protein which the plasma value decrease during infection, injury or stress possibly as a result of increased metabolic need for tissue repair and free radical neutralization . Lower levels of albumin in this study might have been caused also by poor appetite, malnutrition and malabsorption commonly observed in tuberculosis. The lower level of albumin may therefore be one of the complications associated with pulmonary tuberculosis.
According to my study albumin results were very low with group two of drugs combination (RIF,EMB) .

In GGT estimation we found there was increase in it`s level among TB patients under treatment these result was dis agreement with another study (Salma et al, 2015) there was insignificant decrease in the liver enzymes (AST, ALT and GGT). GGT increase as adverse effect of the drugs .According to my study GGT increase with all groups of the drugs but in group two of drug combination (RIF,EMB) give the highest increase .So using of combination of drugs (RIF,EMB) produce risk to

liver and may also cause drug induced hepatotoxicity this result was dis agreement with (Rohit et al, 2009) . Isoniazid and rifampicin given together produce hepatotoxicity more frequently than either drug alone .

5.2 Conclusion

From the results and finding of this study, it is concluded that: The plasma level of albumin was decreased in TB patients under treatment and plasma level of GGT was increased among TB patients and correlation were found between albumin and GGT level.

5.3**Recommendations**

1.Using of Rifampin with Ethumbutol together for treatment of tuberculosis increase risk for liver damage and hepatotoxicity.
2.More studies should be carried out to discover new treatment for TB which do not cause hepatotoxicity.

3.Biochemical screening should be carried out for patients for liver enzyme and albumin before and after treatments.

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Zhang , Y, Yew WW(2009). Mechanisms of drug resistance in Mycobacterium tuberculosis.Int J Tuberc Lung Dis. ;13(11**Appendix I**

Questionnaire

Sudan University of Science and Technology (SUST)

College of Graduate Studies

Assessment of serum GGT and albumin among patients with Tuberculosis under treatments

Patient code ☐

Age ☐ Gender ☐

Residence ☐ Work ☐

Historical review:

Liver problem ☐

Liver surgery ☐

Type of drugs

Rifampin: ☐ Isoniazid: ☐ Pyrazinmade: ☐

Compination ☐ :Ethmbutol: ☐ Stropmycin ☐

Dose of drugs ……..

Duration of drugs …….

Disease since when……..

Progress of disease…….

:Do you experience any of the following

Jundice: ☐ Hepatitis: ☐ HIV ☐

30.