

## **Dedication**

**To**

**My father , sisters , brothers**

**To**

**Whom may god bless me because of her prayers....my mother**

**To**

**The compassionate souls which make my dreams com to realty**

**My husband**

**To**

**The person who denoted her time and energy helping us to achieve  
this study .....my respectful supervisor**

**Dr : Nuha Eljaili Abubker**

**All love to my beautiful son Hussien**

**To**

**The people , whom I love , respect and appreciate**

**To**

**All these dedicated my study**

## **Acknowledgmen**

Thanks are first and last to Allah who enable me to conduct this study by the are grace of him and denoted strength and patience.

Am thanking everybody who contributed to the success of this work.

In particular , am grateful to my supervisor . For her skillful guidance , wisdom , enthusiastic and encouragement through the progress of this

To my family for their patience , encouragement and moral support during this research .

Sincere gratitude extending to my friends , colleagues and relatives who assisted me in one way or another .

Sincere gratitude extending to Alshaab hospital and lab staff .

## Abstract

This study was conducted to measure plasma levels of s( AST, ALT, ALP) liver enzyme in patients with b tuberculosis in Khartoum state . Fifty samples were collected from patients during the period between April to May 2017 , from randomly chosen patients diagnosed with pulmonary tuberculosis un

der taking the treatment for 2 months from Alshaab teaching hospital and fifty apparently healthy individuals serve as control group.

Cobas integra 400 plus was used to estimate plasma levels of ( AST, computer program .

The study results showed that , plasma levels of AST , ALP were significantly increased in patients group compared to control group (mean  $\pm$  SD for cases versus control for (AST,ALP) :  $(32.04 \pm 18.15 \text{ IU}\backslash\text{L}$  ,p-value =0.00)  $(141.02 \pm 145.20 \text{ IU}\backslash\text{L}$  , p-value =0.00) respectively .

The results of this study showed that , there were significantly increased in the levels of plasma AST , ALT , ALP in male patients compared to female (mean  $\pm$  SD) for male versus female  $(43.28 \pm 19.47$  versus  $20.80 \pm 5.51 \text{ IU}\backslash\text{L}$  p-value =0.00) ,  $(28.80 \pm 21.55$  versus  $15.61 \pm 9.10 \text{ IU}\backslash\text{L}$  p-value =0.01) and  $(181.08 \pm 194.30$  versus  $99.96 \pm 42.19 \text{ IU}\backslash\text{L}$  p-value =0.05) respectively .

The results of this study showed that , there was significant decrease in the mean of BMI in patients with pulmonary tuberculosis compared to control group (mean  $\pm$  SD for case versus control  $(0.17 \pm 18.68)$  versus  $(21.54 \pm 1.72)$  , p-value = 0.04) .

common among age between (19-49) years 70% and 30% of patients between age (50-82) years , this disease most abundant in male (60%) than female (40%) .

Person correlation showed no correlation between plasma levels of AST , ALP and age (r = 0.15, p-value =0.30) (r = 0.18 , p-value = 0.77) respectively .

Person correlation showed a significant weak negative correlation between plasma level of ALT and age ( $r = -0.18$  ,  $p\text{-value} = 0.05$ ).

In conclusion : the plasma levels of AST , ALP were significantly increased and there was insignificant difference in ALT in patients with pulmonary tuberculosis under taking the treatment for 2 months in Khartoum state .

## مستخلص الدراسة

اجريت هذه الدراسة لقياس مستويات البلازما من إنزيمات الكبد في المرضى الذين تم تشخيصهم بالاصابه بمرض السل الرئوي تحت العلاج لمدة شهرين في ولايه الخرطوم . تم جمع عينه من المرضى خلال الفتره الممتده من ابريل الى مايو 2017, تم إختبارهم عشوائيا من مستشفى الشعب التعليمي و خمسين من الافراد كمجموعه ضابطه0

تم إستخدام جهاز الكوباس إنتكرا بلس 400 لقياس مستوى إنزيمات الكبد من البلازما ؛ و تم تحليل النتائج بواسطه برنامج الحزمه الإحصائيه للعلوم الإجتماعيه0

و اظهرت الدراسة ان هنالك إرتفاعا معنويا ملحوظ ذو دلالة إحصائيه في مستويات البلازما من إنزيم ناقلات إسبارتات و إنزيم الفوسفاتاز القلوي في المرضى مقارنة بمجموعه الاصحاء (متوسط  $\pm$  الإنحراف المعياري ) 0

لناقلات الإسبارتات : (  $18.15 \pm 32.04$  وحده عالميه ، ومستوى المعنويه = 0.00 )

لفوسفاتاز القلوي : (  $26.2 \pm 77.82$  وحده عالميه ، ومستوى المعنويه = 0.00 )

واظهرت الدراسة ان مستوى إنزيم ناقلات الالنين لم يتغير معنويا في المرضى مقارنة بالاصحاء (متوسط  $\pm$  الإنحراف المعياري) (  $17.67 \pm 22.20$  وحده عالميه ، و مستوى المعنويه = 0.45 )

اظهرت الدراسة ان مستوى إنزيمات الكبد إرتفع معنويا في المرضى الذكور مقارنة بالمرضى الإناث .

إنزيم ناقلات الإسبارتات : (  $19.47 \pm 43.28$  ) مقابل (  $5.51 \pm 20.80$  ) وحده عالميه ، ومستوى المعنويه = 0.00 ) .

إنزيم ناقلات الالنين : (  $21.55 \pm 28.80$  ) مقابل (  $9.10 \pm 15.61$  ) وحده عالميه ، ومستوى المعنويه = 0.01 )

إنزيم الفوسفاتاز القلوي : (  $194.30 \pm 181.08$  ) مقابل (  $42.1 \pm 99.96$  ) وحده عالميه ، ومستوى المعنويه = 0.05 )

واظهرت نتائج الدراسة ان هنالك إنخفاضا معنويا في متوسط مؤشر كتله الجسم لدى المرضى مقارنة بالمجموعه الضابطه ( متوسط مؤشر الكتله  $\pm$  الإنحراف المعياري للمرضى مقابل الاصحاء ) (  $18.68 \pm 0.17$  ) مقابل (  $1.72 \pm 21.54$  ) وحده عالميه ، ومستوى المعنويه = 0.04 ) .

واظهرت الدرأسه ان السل الرئوي أكتر شيوعا بين عمر (17-49) سنه (70%) و (30%) من المرضى الذين تتراوح اعمارهم بين (50-82) سنه وهذا المرض أكتر شيوعا لدى الزكور (60%) ، من الإناث (40%) 0

بينت النتائج في معامل بيرسون للإرتباط عدم وجود إرتباط معنوي بين مستوى البلازما من إنزيم ناقلات الاسبارتات وإنزيم الفوسفات القلوي والعمر (معامل بيرسون لإرتباط = ، 0.15 ، ومستوى المعنويه = 0.30 ) (معامل بيرسون لإرتباط = 0.18 ، ومستوى المعنويه = 0.77) 0

و وجود إرتباط سلبي ضعيف بين مستوى البلازما من إنزيم ناقلات الالنين والعمر (معامل بيرسون لإرتباط = -18.0 ، ومستوى المعنويه = 0.05) 0

في الختام : إرتفعت مستويات البلازما من إنزيمي ناقلات الاسبارتات و الفوسفات القلوي ، ولم يوجد تغير في مستوى البلازما من إنزيم ناقلات الالنين بشكل ملحوظ في المرضى الذين تم تشخيصهم بالسل الرئوي في ولايه الخرطوم 0

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### List of abbreviations

Abbreviations	Full term
AST	Aspartate transaminase
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ATD	Anti-Tuberculosis Treatment
BMI	Body mass index
INH	Isoniazid
LFT	Liver function test
MDR	Multi drug resistance
PZA	Pyrazinamide
RIF	Rifampicin
TB	Tuberculosis
WHO	World health organization

## **1.Introduction**

### **1.1. Introduction**

Tuberculosis is a major public problem world-wide , it is a contagious disease caused by organism mycobacterium tuberculosis , aerobic non-motile bacillus.

Liver enzyme like AST, ALT and ALP play important role in many biological system such as , filter the blood coming from the digestive tract , detoxifies chemical and metabolizes drug , secretes bile and make proteins important for blood clotting and other functions (Anantnarayan *etal .*, 2000).

Deficiency of liver enzymes impairs over all immune function , digestive, toxic , metabolizes and clotting problems.

There is a relationship between TB and liver enzymes , during anti-tuberculosis therapy the levels of liver enzymes such as Alkaline phosphatase (ALP) , serum Glutamic Pyruvate Transaminase (SGPT) , serum Oxaloacetic Transaminase (SGOT) or Aspartate Transaminase (AST) get elevated from its normal range hence cause toxicity or malfunction of human liver (Dinesh , 2005 ).

## **1.2. Rationale**

Tuberculosis is a global public health problem , tuberculosis is the second biggest killer globally . In 2015 , 1.8 million people died from the disease with 10.4 million falling ill.

Change in distribution of liver enzyme in body tissue is known to occur in chronic infection in patients with tuberculosis. Among the first-line drugs , isoniazid (INH) , rifampicin (RIF) and pyrazinamide (PZA) are associated with hepatotoxicity and may result in additional liver damage in patients with preexisting liver disease considering the efficacy of these drugs, however (particularly INH and RIF ),it is generally recommended that they be used if possible, even in presence of all these drugs RIF is least likely to cause hepatocellular damage , although rarely it is associated with cholestatic jaundice of the three agents , PZA is probably the most hepatotoxic.

According to my knowledge there is no published study in Sudan to study plasma levels of liver enzyme in TB patients in Khartoum state.

### **1.3.Objective**

#### 1.3.1.General objective:

To study the plasma levels of AST , ALT and ALP among Sudanese patients with pulmonary tuberculosis in Khartoum state.

#### 1.3.2. Specific objectives :

1-To measure and compare the levels of plasma liver enzymes AST , ALT and ALP in both study groups.

2-To calculate and compare mean of BMI in both study groups.

3-To correlate between the liver enzymes AST , ALT and ALP and study variables (age and gender ) in patients with pulmonary tuberculosis under treatment .

## 2.Literature review

### 2.1.The pulmonary tuberculosis :

Is an infectious disease that usually affects the lungs . compared with other diseases caused by a single infectious agent , tuberculosis is the second biggest killer , globally . In 2015 , 1.8 million people died from the disease , with 10.4 million falling ill . In the 18<sup>th</sup> and 19<sup>th</sup> centuries , a tuberculosis epidemic rampaged throughout Europe and North America , before the German microbiology Robert Koch discovered the microbial causes of tuberculosis in 1882 . Following Kochs discovery , the development of vaccines and effective drug treatment led to the belief that the disease was almost defeated . I need , at one point, the United Nation , predicted that tuberculosis (TB) would be eliminate worldwide by 2025. However in the mid-80s , TB causes began to rise worldwide , so much so , that in 1993 the World Health (WHO) declared that TB was a global emergency the first time that a disease had been labeled as such . fortunately , with proper treatment, the vast majority of cases of tuberculosis are curable . Cases of TB have decreased in the United States since 1993 , but the disease remains a concern without proper treatment , up to two- thirds of people ill with tuberculosis will die (Steele *etal* ., 1991).

#### 2.1.1.Causes of pulmonary tuberculosis :

The Mycobacterium tuberculosis bacterium causes TB. It is spread through the air when a person with TB (whose lungs are affected) coughs , sneezes , spits laughs , or talks. TB is contagious , but it is not easy to catch . the chances of catching TB from someone you live or work with are much higher than from a stranger . Most people with active TB who have received appropriate treatment for at least 2 weeks are no longer contagious . Since antibiotics began to be used to fight TB , some strains have become resistant to drug . Multidrug-resistant TB (MDR-TB) arises when an antibiotic fails to kill all of the bacteria , with the surviving bacteria developing resistance to that antibiotic and often others at the same time . MDR-TB is treatable and curable only with the use of very specific anti-TB drugs , which are often limited or not readily available .



In 2012 around 450,000 people developed MDR-TB (Bhandari *et al.* , 2013).

### **2.1.2. Symptoms of tuberculosis :**

While latent TB is symptomless , the symptoms of active TB include the following :-

Coughing sometimes with mucus or blood , chills , fever , loss of weight , loss of appetite and night sweats .

Tuberculosis affects the lungs , but can also affect other parts of the body. When TB occurs outside of the lungs , the symptoms vary accordingly . Without treatment , TB can spread to other parts of the body through the bloodstream :-

TB infecting the bones can lead to spinal pain and joint destruction

TB infecting the brain can cause meningitis

TB infecting the liver and kidneys can impair their waste filtration functions and lead to blood in the urine

TB infecting the heart can impair the hearts ability to pump blood , resulting in a condition called cardiac tamponed that can be fatal (Saukkonen *et al.* , 2006 ).

### **2.1.3. Diagnosis of tuberculosis :-**

To check for TB, stethoscope to listen to the lungs and check for swelling in the lymph nodes. Symptoms and medical history as well as assessing the individuals risk of exposure to TB . The most common diagnostic test for TB is a skin test where a small injection of PPD tuberculin , an extract of the TB bacterium , is made just below the inside forearm . The injection site should be checked after 2-3 days , and , if a hard , red bump has swollen up to a specific size , then it is likely of TB is present .

Unfortunately , the skin test is not 100 percent accurate and has been known to give incorrect positive and negative readings . However , there are other tests that are available to diagnose TB . Blood tests , chest X-rays and sputum tests can all be used to test for the presence of TB may be used alongside a skin test . MDR-TB is more difficult to diagnose than

regular TB . It is also difficult to diagnose regular TB in children ( Bhandari , 2013 ) .

#### **2.1.4. Treatments for tuberculosis :-**

The majority of TB cases can be cured when the right medication is available and administered correctly . The precise type and length of antibiotic treatment depends on a persons age , overall health , potential resistance to drugs , whether the TB is latent or active , and the location of infection ( i.e. the lungs , brain , kidneys ) people with latent TB may need just one kind of TB antibiotics , whereas people with active TB ( particularly MDR-TB ) will often require a prescription of multiple drugs (Bhandari , 2013 ) .

Antibiotics are usually required to be taken for a relatively long time . The standard length of time for a course of TB antibiotics is about 6 months . TB medication can be toxic to the liver , and although side effects are uncommon , when they do occur , they can be quite serious. Potential side effects should be reported to a doctor and include :-

Dark urine , fever , jaundice , loss of appetite , nausea and vomiting .

It is important for any course of treatment to be completed fully , even if the TB symptoms have gone away any bacteria that have survived the treatment could become resistant to the medication that has been prescribed and could lead to developing MDR-TB in the future . Directly observed therapy (DOT) may be recommended . This involves a healthcare worker administering the TB medication to ensure that the course of treatment is completed (Bhandari , 2013 ) .

#### **2.1.5. Anti-Tuberculosis Drugs :-**

ATD consists of first-line and second-line drugs . Among the first-line drugs isoniazid (INH) , rifampicin (RIF) and pyrazinamide (PZA) are associated with hepatotoxicity and may result in additional liver damage in patients with preexisting liver disease considering the efficacy of these drugs, however (particularly INH and RIF) , it is generally

recommended that they be used if possible, even in presence of all these drugs RIF is least likely to cause hepatocellular damage , although rarely it is associated with cholestatic jaundice of the three agents , PZA is probably the most hepatotoxic ( Bhandari , 2013 ) .

### **First-line drugs :-**

INH is a bactericidal drug , which is effective against both intra-and extra-cellular organisms since it inhibits the synthesis of mycolic acids in the bacterial cell wall . It is an important and integral part of most anti-mycobacterial regimes . In the early 1970 it became apparent that severe hepatic injury leading to death may occur in some individuals receiving INH ( Garibaldi *etal .* , 1972) .

Additional studies in adults and children have confirmed this , the characteristic pathological process being bridging and multilobular necrosis . INH-induced hepatotoxicity is seen mainly as hepatocellular steatosis and necrosis , and it has been suggested that toxic INH metabolites may bind covalently to cell macromolecules (Tostmann *etal .* , 2008 ) .

Approximately 0.5% of all patients treated with INH monotherapy develop clinically important increases in aminotransferase levels (Tostmann *etal .* , 2008 ) .

In patient who are receiving combination therapies that include INH but not RIF , the incidence of hepatotoxic effects is a round 1.6 % ; the corresponding value for regimens containing both INH and RIF is 2.5 % ( Steele *etal .* , 1991 ) .

INH itself is not hepatotoxic ; toxicity is mediated through its metabolite , hydrazine INH is metabolized in the liver through two main pathways . Acetyl hydrazine , a non toxic metabolite , is formed when metabolism proceeds along the N-acetyltransferase2 (NAT2) pathway while hydrazine , the toxic metabolite , is formed when it proceeds along the amidase pathway (Self *etal .* , 1999 ) .

These enzymes are stimulated by RIF and other enzyme inducers that potentiate the hepatotoxic effects of INH (Senousy *et al.* , 2010) .

Asymptomatic , self-limited increase in aminotransferase levels is observed in the majority of patients treated with INH , which dose not progress to more serious forms of liver injury ( Tostmann *et al.* , 2008 ) .

Presence of jaundice , encephalopathy and the presence of severe hepatitis (aminotransferase levels 10-fold ) are associated with a poor outcome (Moulding , 1992 ) .

Approximately 5-10% of patients who have clinical symptoms of severe hepatitis including jaundice develop acute liver failure ( Verma *et al.* , 2009 ) .

Age appears to be the most important factor in determining the risk of INH-induced hepatotoxicity . Hepatic damage is rare in patients less than 20 years old ; it is observed in 0.3% of those in the 20-34 years age group , increasing to 1.2% in the 35-49 years age group and 2.3% in those older than 50 years of M.B. (Isoniazid-associated hepatitis , 2009) .

Up to 12% of patients receiving INH may have elevated plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities (Bass *et al.* , 1994) .

Recent treatment studies have reported significant transaminase elevation in 1-4% of those treated with INH for latent tuberculosis infection (Bailey *et al.* , 1974 ) .

A meta-analysis of six studies estimated the rate of clinical hepatitis in patients given INH alone to be 0.6% (American Thoracic Society of America Treatment of tuberculosis ) . A large survey estimated the rate of fatal hepatitis to be 0.023% , but more recent studies suggest the rate is substantially lower (Millard *et al.* , 1996 ) .

Hepatotoxicity due to INH therapy seems to be idiosyncratic in most patients and does not recur with challenge , hence can be reintroduced after complete clinical recovery . A few cases may be due to allergic-type

hypersensitivity reactions with prominent eosinophilia and rash (Gent *et al* ., 1992 ) .

While testing baseline and follow-up serum ALT and bilirubin levels before beginning INH therapy is desirable in all patients , it is strongly recommended for patients with an underlying liver disorder such as chronic hepatitis and cirrhosis , in patients who regularly consume alcohol , those with HIV infection being treated with HAART , pregnant women , and those who are up to 3 months postpartum ( Saukkonen *et al* ., 2006) .

INH should be discontinued when jaundice and/or hepatitis symptoms are reported and ALT is at least three times the ULN , or if ALT is at least five times the ULN in the absence of symptoms (American Thoracic Society , 2000 ) . Most hepatitis occurs 4-8 weeks after the start of therapy . INH should be administered with great care to those with preexisting hepatic disease (Saukkonen *et al* ., 2006 ) .

### **Rifampicin :-**

RIF is bactericidal agent which inhibits mycobacterial DNA-dependent RNA polymerase . RIF is primarily metabolized by acetylation and glucuronidation ; metabolites are excreted in the bile . Hepatotoxicity associated with RIF is usually idiosyncratic (Verma *et al* ., 2009 ) .

RIF may occasionally cause dose-dependent interference with bilirubin uptake due to competition with bilirubin for clearance at the sinusoidal membrane , resulting in mild , asymptomatic unconjugated hyperbilirubinemia or jaundice without hepatocellular damage . Conjugated hyper bilirubinemia probably results from RIF inhibiting the major bile salt exporter pump , impeding secretion of conjugated bilirubin at the canalicularlevel (Byrne *et al* ., 2002 ) .

This may be transient and occurs early in treatment or in some individuals with preexisting liver disease (Capelle *et al* ., 1972 ) .

Occasionally RIF can cause hepatocellular injury and can potentiate hepatotoxicity of other ATD (Byrne *et al.*, 2002 ) .

In patients with primary biliary cirrhosis , in whom baseline transaminases were significantly elevated , clinically significant hepatitis was attributed to RIF in 7.3 and 12.5% of patients (Menzies *et al* ., 2004).RIF can cause hepatocellular changes such as centri-lobular necrosis , associated with cholestasis . Histopathological findings range from spotty to diffuse necrosis , lymphocytic infiltration , focal cholestasis , increased fibrosis , and micro-nodular cirrhosis have been seen in patients with RIF-and PZA-induced hepatotoxicity . Idiosyncratic hypersensitivity reaction to RIF , manifested as anorexia , nausea , vomiting , malaise , fever , mildly elevated ALT , and elevated bilirubin , usually occurs in the first month of treatment initiation . published tuberculosis-related studies have assessed RIF alone for treatment of latent tuberculosis , and all these studies confirm the low rate of hepatotoxicity of RIF chiefly manifested as asymptomatic elevation of transaminase , Chronic liver disease , alcoholism , and old are appear to increase the incidence of severe hepatic problems when RIF is given alone or concurrently with INH (Saukkonen *et al* ., 2006 ) .

### **Ethambutol :-**

EMB is bacteriostatic antibiotic approved for the treatment of mycobacterial infection . it works by preventing the formation of the bacterial cell wall . Mycolic acid attach to the 5~-hydroxyl groups of D-arabinose residues of arabinogalactan-peptidoglycan complex in the cell wall . EMB disrupts arabinogalactan synthesis by inhibits the formation of this complex and leads to increased permeability of the cell wall . hepatotoxic effects of this agent are not of major concern (Saukkonen *et al* ., 2006 ).

### **Second line-drugs :-**

They can be used if either hepatotoxic effects or multidrug resistance develop during first line-therapy . Streptomycin is a bactericidal aminoglycoside antibiotic , which is considered safe to use in patients with an underlying liver disease . Capreomycin , like streptomycin , is not metabolized by the liver and is eliminated unchanged through the kidneys They are considered safe for use in patients who have an underlying liver disease and as a second-line therapy if hepatotoxic effects developin

patients treated with first line anti-tuberculosis drugs . Cycloserine also has no reported hepatotoxic effects . However , in patients with alcoholic hepatitis , an interaction between alcohol and cycloserine can lead to an increased risk of seizures ( Snavely *et al .* , 1984 ) .

Quinolones ( levofloxacin , moxifloxacin and gatifloxacin ) are currently considered fairly safe , and their pharmacokinetics do not seem to be altered in patients who have advanced liver disease . Hepatotoxic effects associated with quinolones are usually mild and reversible ( Wolfson *et al .* , 1991 ) .

### **2.1.6. Prevention of tuberculosis :-**

A few general measures can be taken to prevent the spread of active TB . Avoiding other people by not going to school or work , or sleeping in the same rooms as someone , will help to minimize the risk of germs from reaching anyone else . Wearing a mask , covering the mouth , and ventilating rooms can also limit the spread of bacteria ( Wolfson *et al .* , 1991 ) .

## **2.2. The liver :-**

The liver is large , meaty organ that sits on the right side of the belly . Weighing about 3 pounds , the liver is reddish-brown in color and feels rubbery to the touch .protected by the rib cage .the liver has two large sections , called the right and the left lobes . the gallbladder sits under the liver , along with parts of the pancreas and intestines . liver works cited there are no sources in the current document . Together to digest , absorb and process food . main job is to filter the blood coming from the digestive tract , before passing it to the rest of body and detoxifies chemicals and metabolizes drugs . As it does so , the liver secretes bile that ends up back in the intestines . and also makes proteins important for blood clotting and other functions (Bhandari , 2013 ) .

### **2.2.1. Liver enzymes :-**

Are useful biomarkers of liver injury in a patient with some degree of intact liver function . Most liver disease cause only mild symptoms initially , but these disease must be detected early . Hepatic involvement

in some disease can be of crucial importance . this testing is performed in blood sample.

### **AST and ALT:-**

AST , also called serum glutamic oxaloacetic transaminase or aspartate aminotransferase , is similar to ALT in that it is another enzyme associated with liver parenchymal cells . it is raised in acute liver damage , but is also present in red blood cells , and cardiac and skeletal muscle , so is not specific to the liver . the ratio of AST to ALT is mostly useful in differentiating between causes of liver damage ( Nyblom *et al* . , 2004 ) .

Elevated AST levels are not specific for liver damage and AST has also been used as a cardiac marker . when the AST is higher than ALT , a muscle source of these enzymes should be considered . for example , muscle inflammation due to dermatomyositis may cause  $AST > ALT$  . this is a good reminder that AST and ALT are not good measures of liver function because they do not reliably reflect the synthetic ability of the liver and they may come from tissues other than liver (such as muscle)  $AST/ALT$  elevations instead of ALP elevations favor liver cell necrosis as a mechanism over cholestasis . When AST and ALT are both over 1000 IU/L , the differential can include acetaminophen toxicity , shock or fulminant liver failure. When AST and ALT are greater than three times normal but not greater than 1000 IU/L , the differential can include alcohol toxicity viral hepatitis, drug-induced liver disease , liver cancer , sepsis , Wilson disease , post-transplant rejection of liver autoimmune hepatitis and steato hepatitis .  $AST/ALT$  levels elevated minimally may be due to rhabdomyolysis among many possibilities ( Lee , 2011) .

### **ALP:-**

Alkaline phosphatase (ALP) is an enzyme in the cells lining the biliary ducts of the liver . ALP levels in plasma rise with large bile duct obstruction , intra-hepatic cholestasis , or infiltrative disease of the liver . ALP is also present in bone and placental tissue , so it is higher in growing children ( as their bones are being remodeled ) and elderly patients with Paget's disease . in the third trimester of pregnancy , ALP is about two to three times higher , Biliary tract disease produces relatively



greater increases in ALP than increases in ALT , AST or LD. ALP is associated with the plasma membrane of hepatocytes adjacent to the biliary canaliculus . obstruction or inflammation of the biliary tract results in an increased concentration of the ALP in the circulation . similar to ALT and AST , ALP is released by osteoblasts , the ileum and the placenta . ALP is elevated : 1 in children 2-to3-fold over adults because the child's skeleton is growing , with bone disease involving osteoblasts ( e.g., metastatic cancer or following a fracture in hyperparathyroidism where parathyroid hormone stimulates osteoblasts through a series of steps that enhances bone resorption ( e.g., parathyroid adenoma or hyperplasia , or secondary hyperparathyroidism from vitamin D deficiency or renal disease ) . and in cases of ileal disease. During the third trimester of pregnancy because the placental isoenzyme is elevated ( Lee , 2011 ).

### **3. Materials and methods**

#### **3.1. Materials :-**

##### **3.1.1. Study approach :**

Quantitative method was used to estimate liver enzymes in Sudanese patients with tuberculosis under treatment for two month in Khartoum state . during the periods from March to April 2017 .

##### **3.1.2. Study design :**

This was a cross sectional hospital base case control study .

##### **3.1.3. Study area :**

This study was conducted in Shaab Teaching hospital in Khartoum states.

##### **3.1.4. Study population :**

This study included 50 Sudanese patients with pulmonary tuberculosis in Khartoum state under treatment and 50 healthy individuals as control .

##### **3.1.5. Sample size :**

This study included one hundred volunteered to participate in this study (50 patients and 50 apparently healthy individuals serve as control age and sex matched with case group ) .

##### **3.1.7. Exclusion criteria :**

Patients with liver disease , bone disease , renal disease , muscle disease and patients with other disease that affect the levels of plasma liver enzymes .

##### **3.1.8. Sample collection and processing :**

3 ml of blood samples from all participants were taken by vein puncture using disposable syringes . The blood samples transferred in to anticoagulant container (Lithium heparin ) . plasma was separated from

blood cells after centrifugation for 5 minutes at 5000 r. p. m , at room temperature .

### **3.1.9. Ethical consideration :**

Verbal consent was taken regarding acceptance to participate in the study .Before the specimen was collected , the donor knew that this sample was collected for research purpose .

### **3.1.10. Data analysis :**

Differences in means were tested with an independent T test . The SPSS ( Statistical Package for Social Sciences ) were used for all statistical analysis and  $p\text{-value} \leq 0.05$  considered significant .

### **3.1.11. Data collection:**

The clinical data were obtained from history ; clinical examination and hospital follow up records and were recorded on a questionnaire sheet (appendix 1) .

## **3.2. Methods :**

### **3.2.1. Estimation of ALP :**

#### **3.2.1.1. Principle of the method :**

ALP catalyzes the hydrolysis of organic phosphate of paranitrophenyl phosphate (PNPP) at PH 10.3 , to liberate inorganic phosphate (Pi) and paranitrophenol which absorbed at 405 nm . The increase absorbance of paranitrophenol at 504nm is directly proportional to the ALP activity ( appendix 11) .

### **3.2.2. Estimation of AST :**

#### **3.2.2.1. Principle of the method :**

AST catalyzes the transformation of amino group from L-Aspartate to alpha-Ketoglutarate at PH 7.8 , to form glutamate and oxaloacetate the latter reduced to malate by malate dehydrogenase (MDH) in presence of

NADH (as coenzyme) . The catalytic rate of reaction is monitored kinetically at 340 nm . The decrease absorbance of NADH at 340 nm by the decrease absorbance of NADH to NAD which is directly proportional to the AST activity ( appendix 111) .

### **3.2.3. Estimation of ALT :**

#### **3.2.3.1. Principle of the method :**

ALT catalyzes the transformation of amino group from L-Alanine to alpha-Ketoglutarate at PH 7.8 , to form glutamate and pyruvate the latter reduced to lactate by lactate dehydrogenase (LDH) in presence of NADH ( as coenzyme) . The catalytic rate of reaction is monitored kinetically at 340 nm . The decrease absorbance of NADH at 340 nm by the decrease absorbance of NADH to NAD which is directly proportional to the AST activity ( appendix 1V) .

### **3.3. Quality control :**

The precision and accuracy of all methods used in this study were checked by commercially prepared normal and pathological control sera .

### **3.4. Statistical analysis :**

Data obtained from this study was analyzed by using Statistical Package for Social Sciences ( SPSS) .

## 4. Results

**Table (4-1) :** Comparison of AST, ALT and ALP in study groups.

( AST , ALP ) were significantly increased in patients with pulmonary tuberculosis compared to control group .

There was insignificant difference in the mean of ALT in patients compared to control group .

**Table (4-2 ) :** Comparison of AST, ALT and ALP in male and female.

There was significant increased in the mean of plasma levels of liver enzymes AST, ALT and ALP in male compared to female .

**Table (4-3 ) :** Mean of BMI in study groups .

The mean of BMI was significant decreased in patients with pulmonary tuberculosis compared to control group .

**Figure (4-1 ) :** Age distribution in case group.

70% of patients at age range (19-49 ) years ( group A ) and 30% of patients at age range (50-82 ) years ( group B ) .

**Figure (4-2 ) :** Gender distribution in case group.

60% of patients were male , while 40% of patients were female.

**Figure (4-3 ) :** Correlation between AST level and age in case group.

There was no correlation between AST level and age .

**Figure (4-4 ) :** Correlation between ALT level and age in case group.

There was a significant weak negative correlation between ALT level and age .

**Figure (4-5 ) :** Correlation between AST level and age in case group.

There was no correlation between AST level and age .

**Table (4-1) :** Comparison of AST, ALT and ALP in study groups.

Variables	Patients N= 50 Mean $\pm$ SD	Control N= 50 Mean $\pm$ SD	P-value
AST (U\L)	32.04 $\pm$ 18.15	25.38 $\pm$ 15.33	0.00
AST (U\L)	22.20 $\pm$ 17.67	16.26 $\pm$ 7.33	0.45
ALP (U\L)	141.02 $\pm$ 145.20	77.82 $\pm$ 26.20	0.00

Result given in mean  $\pm$  SD

P-value  $\leq$  0.05 consider significant

**Table (4-2) :** Comparison of AST, ALT and ALP in male and female.

Variables	Male Mean $\pm$ SD	Female Mean $\pm$ SD	P-value
AST (U\L)	39.37 $\pm$ 19.93	21.05 $\pm$ 5.64	0.00
AST (U\L)	26.37 $\pm$ 20.40	15.95 $\pm$ 10.08	0.02
ALP (U\L)	167.50 $\pm$ 181.68	101.30 $\pm$ 34.97	0.05

Result given in mean  $\pm$  SD

P-value  $\leq$  0.05 consider significant

**Table (4-3) :** Mean of BMI in study groups

**Table (4-3 ) : Mean of BMI in study groups**

Variables	Case Mean $\pm$ SD	Control Mean $\pm$ SD	P-value
BMI	18.68 $\pm$ 0.17	21.54 $\pm$ 1.27	0.04

Result given in mean  $\pm$  SD

P-value  $\leq$  0.05 consider significant

## 5. Discussion , Conclusions and Recommendations

### 5.1. Discussion :

Pulmonary tuberculosis is a global disease affecting about 1\3 third of the worlds population with its attendant mortality and morbidity ( park , 2007) . Pulmonary tuberculosis can affect many substances in the body by decreasing or increasing them , this study conducted to get the effect of pulmonary tuberculosis under treatment on the levels of plasma liver enzymes (AST , ALT , ALP ) in Khartoum state .

From the finding of this study as appears in table (4-1) ; The levels of liver enzymes (AST , ALP ) were significantly increased in case group compared to control group . (P-value = 0.00 , 0.00) respectively. the elevated levels of this enzymes due to the first line drugs (INH , RIF , PZA ) which are associated with hepatotoxicity and may result in liver damage compared to control group and there was insignificant difference in the level of ALT in both study group . (p-value = 0.45) observed in patients compared with control group . This result agreed with results done by (Mythili *etal .* , 2016 ) , which showed that ; plasma level of liver enzymes (AST , ALP) increase in case compared to control group .

Also the results in agreement with another studies carried by many authors ( Modawe *etal .* , 2014 ; Danburam *etal .* , 2012 ; Mythili *etal .* , 2016 ) , which finding confirmed that , patients with pulmonary tuberculosis at greater risk of development of high plasma enzymes levels

And place them at risk of developing life threatening situation .

The results of this study showed that , there were significantly increased in the levels of liver enzymes (AST, ALT , ALP ) in male patients with tuberculosis compared to female patients (P-value 0.00 , 0.01 , 0.05) .This result is agreed with previous study carried by (Danburam *etal .* , 2012 ) which showed that ; plasma levels of liver enzymes ( AST , ALT ,ALP ) are increased in male compared to female . Also the results in agreement with another results done by ( Preeti *etal .* , 2013 ) which show elevated levels of liver enzymes in male patients compared to female .



The results of this study showed that , there was significant decreased in BMI in patients with pulmonary tuberculosis compared to control group (p-value = 0.00 ) .

This result agreed with study done in Indonesia and Malawi ( Karyadi *etal .*, 2000 ; Van , 2004 ) . which showed low BMI in patients with pulmonary tuberculosis and this may be due to poor dietary intake , in appetite , anorexia , and impaired absorption or increased catabolism . Also the result agreed with another result done by a(Hopwell ., 1994) . low BMI is known risk factor for mortality .

Also pulmonary tuberculosis are most common among age (19-49) years.

These results in agreement with previous study, which showed that pulmonary tuberculosis infection is common among age (19-50) (Mythili *etal .*, 2016 ) . The finding obtained from especially designed questionnaire revealed that , the majority of patients with pulmonary tuberculosis participants in this study were male (60%) while female was (40% ) . These results in agreement with previous study which showed that pulmonary tuberculosis infection is more common in males than females (Danburam *etal .*, 2012) .

Also the result showed that , there were no correlation between ( AST , ALP ) levels and age (  $r= 0.15$  , p-value 0.30 ) (  $r= 0.18$  , p-value 0.77 ) respectively . This result agreed with another result , which showed that , there were no correlation between ( AST , ALP ) levels and age (Karyadi , 2007 ) . This result disagreed with another result , which found , age appears to be the most important factor that affect liver function , hepatic damage is rare in patients less than 20 years old ; it is observed in 0.3% of those in the 20-34 years age group , increasing to 1.2% in the 35-49 years age group and 2.3% in those older than 50 years . ( Isoniazid-associated hepatitis , 2009 ) .

The result showed that , there was weak negative correlation between ALT level and age . (  $r= -0.18$  , p-value =0.05 ) . This result agreed with another result , which showed there was weak negative correlation between ALT level and age ( Karyadi , 2007 ) .

## **5.2. Conclusion**

According to the results of this study it is concluded that :

Plasma liver enzymes AST and ALP levels are significantly increased in patients with pulmonary tuberculosis . and there is no difference in the level of ALT in patients with pulmonary tuberculosis .

BMI is significantly decreased in patients with pulmonary tuberculosis .

There is a weak negative correlation between ALT level and age .

### **5.3. Recommendations**

From the finding of this study it is recommended that :  
Liver enzymes should be done as routine investigations in pulmonary tuberculosis to avoid serious complications of disease .

More studies should be carried out on the effect of pulmonary tuberculosis on plasma levels of enzymes concentration with other liver function test parameters .