Sudan University of Sciences andTechnology

Faculty of Graduate Studies

Determining Normal Liver Stiffness in Khartoum State Population by Ultrasonography

تحـــديد الصـــلابة الطبيـــعية للكـبد لسكان ولاية الخرطوم بإستخدامالتصوير بالموجات الصوتية

A ThesisSubmitted For Partial Fulfillment for the Requirements of M.Sc. Degree in Medical Diagnostic Ultrasound

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قال تعالى:

صدق الله العظيم

البقرة (285-286)

DEDICATION

To

Mymother

A strong and gentle soul who taught me to trust in Allah, believe in hard work and that so much could be done with little

My father

For earning an honest living for us and for supporting and encouraging me to believe in myself

My beloved siblings

Along with all hard working and respected teachers

Thank you all…

ACKNOWLEDGEMENT

Sincere gratitude is hereby extended to everyone who never ceased in helping me until this research is structured.
Full regard for my supervisor**Dr. Asma Ibrahim Ahmed** for sharing her precious time and positive insights that motivated me to complete work in success.
Above all, utmost appreciation to Almighty Allah for the divine intervention in this academic endeavor.

ABSTRACT

This is a descriptive, cross sectional study which was done during July to September 2016 and was carried out at Aliaa Specialized Hospital, Khartoum-Sudan. The study discusses determining normal liver stiffness in Khartoum state population using ultrasonography. A total of “115” healthy Sudanese cases were selected randomly and aged between 5-66 years. Any cases with diabetes mellitus, or any underlying liver disease was excluded from this study. All cases were subjected to be examined using Fibroscan machine manufactured by Echosens (Paris, France). Data was collected using a data collection sheet and data analysis was done by SPSS. The study reported liver stiffness values in relation to age and in relation to gender.

The study found that in 3 patients aged (5-18) years, the mean of the liver stiffness measurement LSM was[4.667±1.1547] kPa. In 26 patients aged (19-29) years the mean of the LSM was [5.035 ±1.0284] kPa. In 33 patients aged (30-40) years the mean of the LSM was [5.291 ±1.0596] kPa. In 29 patients aged (41-51) years the mean of the LSM was [5.986 ±1.2589] kPa. In 24 patients aged (52-66) years the mean of the LSM was [5.029 ± 0.9671] kPa. The overall mean of the LSM in 115 patients was [5.34 ± 1.144] kPa.

The result after data analysis found that the healthy liver stiffness range is 3.5 to 7.8 kPa. There is no significant correlation between LSM and age. The mean of the LSM for female [5.588 ± 1.1847] kPa, is slightly higher than mean of the LSM for male [5.237± 1.1188] kPa.

It is important to know the reference value of the liver stiffness in Sudanese population, to state the pathology easily. Further studies should be done using a larger sample size.

مستخلص الدراسة

هذه دراسة وصفية مقطعية تم القيام بها خلال الفترة من يوليو حتى سبتمبر 2016 وأجريت في مستشفى علياء التخصصي بالخرطوم- السودان. الدراسة تتناول تحديد صلابة الكبد لسكان ولاية الخرطوم باستخدام التصوير بالموجات الصوتية. مجموعة من 115 حالة تم اختيارهم بشكل عشوائي وتتراوح اعمارهم بين 5-66 سنة. تم استبعاد اي حالات تعاني من داء السكري او اي داء يصيب الكبد بشكل اساسي. تم اخضاع جميع الحالات للفحص باستخدام جهاز الفايبروسكان المصنع من قبل شركة ايكوسنس في باريس- فرنسا. وقد تم جمع البيانات باستخدام ورقة جمع البيانات وتم تحليلها باستخدامبرنامج متخصص. ذكرت الدراسة قيم صلابة الكبد تبعا للعمر وعلى اساس نوع الجنس.

ووجدت الدراسة انه في 3 حالات تتراوح أعمارهم بين (5-18) سنة، كان متوسط صلابة الكبد يعادل [4.667 ± 1.1547] كيلو باسكال. وفي 26 حالة تتراوح أعمارهم بين (19-29) سنة كان متوسط صلابة الكبد يعادل [5.035 ± 1.5284] كيلو باسكال. وفي 33 حالة تتراوح أعمارهم بين (30-40) سنة كان متوسط صلابة الكبد يعادل [5.291 ± 1.0596] كيلو باسكال.وفي 29 حالة تتراوح أعمارهم بين (41-51) سنة كان متوسط صلابة الكبد يعادل [5.986 ± 1.2589] كيلو باسكال. وفي 24 حالة تتراوح أعمارهم بين (52-66) سنة كان متوسط صلابة الكبد يعادل [5.029 ± 0.9671] كيلو باسكال. وكان المتوسط العام لصلابة الكبد في 115 حالة [5.34 ± 1.144] كيلو باسكال.

وجدت الدراسة ان مدى صلابة الكبد يتراوح بين (3.5-7.8) كيلو باسكال. وانه لا توجد علاقة بين مدى صلابة الكبد والعمر.ووجد أن متوسط صلابة الكبد للإناث [5.588 ± 1.1847] كيلو باسكال أعلى قليلا من متوسط صلابة الكبد للذكور [5.237 ± 1.1188] كيلو باسكال.

من المهم ان تحدد قيمة مرجعية لصلابة الكبد في الشعب السوداني، لمعرفة الأمراض بسهولة. وينبغي أن يتم إجراء المزيد من الدراسات باستخدام حجم عينة أكبر.

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ABBREVIATIONS

Abbreviation	Full meaning
ARFI	Acoustic radiation force impulse
FS	Fibroscan
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
Hz	Hertz
IGF	Insulin-like growth factor
Kg	Kilogram
kPa	Kilo pascal
LB	Liver biopsy
LS	Liver stiffness
LSM	Liver stiffness measurement
PP	Peak to peak
SD	Standard deviation
SPSS	Statistical package for social sciences
TE	Transient elastography
VCTE	Vibration controlled transient elastography

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CHAPTER ONE

INTRODUCTION

Chapter one

1.2 Introduction

All chronic liver diseases whether of toxic, genetic, autoimmune or infectious origin undergo typical histological changes that ultimately lead to fibrosis/cirrhosis, and the excess deposition of matrix.(Sebastian Mueller, 2003).

Ultrasound imaging plays a major role in the diagnosis, monitoring and therapeutic decisions of chronic liver diseases. It has many clinical indications: morphological examination of the liver parenchyma and assessment of the risk of chronic liver disease by investigating for signs of dysmorphism and/or portal hypertension; detecting and characterizing liver lesions; monitoring local treatments (such as percutaneous radiofrequency) and assessment of treatment response.(N. Frulio, 2013).

Staging liver fibrosis in patients with chronic liver disease is essential for patient management as it allows firstly to identify the severity of the liver damage in order to decide whether or not to start treatment (chronic viral liver disease) to avoid progression to cirrhosis when the fibrosis becomes significant. Secondly to assess the progression or regression of liver fibrosis during treatment.

Lastly to institute specific monitoring to screen for and treat complications (HCC, oesophageal varices) in patients suffering from cirrhosis and even severe fibrosis.(N. Frulio, 2013).

Although liver biopsy remains the gold standard for assessing liver fibrosis, patients may be unwilling to undergo a biopsy procedure and clinicians may be reluctant to advocate it because of the potential adverse effects associated with this invasive procedure. (Froehlich F, 1993).

Despite its diagnostic utility, LB has several limitations, including patient reluctance, adverse events, accessibility, effective cost, sampling error, and intra- and inter-observer variability. Moreover, considering the fact that fibrosis is heterogeneously distributed in the liver, liver biopsy has been criticized because it evaluates only 1/50,000 of the total volume of the liver, due to the small volume of the tissue. For these reasons this technique is becoming increasingly challenged. For these reasons, non-invasive methods to assess liver fibrosis have been developed as an alternative to liver biopsy.(N. Frulio, 2013).

In the past decade, liver stiffness measurement (LSM) using transient elastography has become one of the most viable alternative non-invasive methods to biopsy in assessing liver fibrosis. Previous studies have documented the diagnostic accuracy of the LSM in grading fibrosis for a variety of chronic liver diseases. In addition, LSM has been shown to have prognostic significance in predicting long-term outcome, and in the assessment of treatment response. One of the earliest key concepts of LSM to evolve is that different optimal liver stiffness cut-off values correspond to different stages of fibrosis, and these cut-off values are disease-specific. Although cut-off values for advanced fibrosis and cirrhosis have been well established for different diseases, the normal reference ranges of LSM in specific population groups have not been well defined, especially from large population studies. Histology from normal liver is rarely available, therefore normal ranges of liver stiffness is much harder to establish. (James Fung, 2008).
An earlier small-scaled study using normal livers from subjects undergoing donor hepatectomy have identified a normal cut-off liver stiffness of < 7.2 kPa. (Fung J, 2008).

1.2 Problem of study:

For patients with chronic liver disease, different optimal liver stiffness values correspond to different stages of fibrosis, which are specific for the underlying liver disease and population.

Conventional imaging techniques do not provide information on tissue mechanical properties although its stiffness may vary considerably. In addition, many diseases can lead to changes in tissue stiffness: tumors (particularly malignant) are generally stiffer than the normal surrounding tissue; fibrosis also causes a change in the liver stiffness .So defining the normal liver stiffness by transient elastography in Sudanese population, can estimate reference value in different age group and gender.

1.3 Study Justification:

Assessment of liver fibrosis is important in diagnosis and treatment of chronic liver diseases. This study was conducted to find out the range of liver stiffness in Sudanese population with different age group and gender.

1.4 Objectivesof the study:

1.4.1 General objective:

Defining normal liver stiffness in Khartoum state population by ultrasonography.

1.4.2 Specific objectives:

1. To measure the liver stiffness.
2. To estimate reference value of liver stiffness for Sudanese.

3. To correlate the of liver stiffness with age.
4. To correlate the of liver stiffness with gender.

1.5 Overview of the study :

This study is fall into five chapters. Chapter one consists of introduction about liver stiffness, problem of the study, justification, objectives and the overview of the study. Chapter two presents comprehensive literature review about different measurement studies. While chapter three details the methodology which includes material used to collect the data and methods of data acquisition and analysis. Chapter four includes the presentation of the results using tables and figures. And finally chapter five includes discussion, conclusion and recommendation.

CHAPTER TWO

LITERATURE REVIEW

Chapter two

Literature review

2.1 Liver Structure

The liver is a reddish brown wedge-shaped organ with four lobes of unequal size and shape. A human liver normally weighs 1.44–1.66 kg (3.2–3.7 lb).(Cotran,2005).

It is both the heaviest internal organ and the largest gland in the human body. Located in the right upper quadrant of the abdominal cavity, it rests just below the diaphragm, to the right of the stomach and overlies the gallbladder.(Tortora, 2008).

The liver is connected to two large blood vessels: the hepatic artery and the portal vein. The hepatic artery carries oxygen-rich blood from the aorta, whereas the portal vein carries blood rich in digested nutrients from the entire gastrointestinal tract and also from the spleen and pancreas.These blood vessels subdivide into small capillaries known as liver sinusoids, which then lead to a lobule.(Vinay Kumar, 2015).

Lobules are the functional units of the liver. Each lobule is made up of millions of hepatic cells (hepatocytes) which are the basic metabolic cells. The lobules are held together by fine areolar tissue which extends into the structure of the liver, by accompanying the vessels (veins and arteries) ducts and nerves through the hepatic portal, as a fibrous capsule called Glisson's capsule. (Dorland, 2012).

The whole surface of the liver is covered in a serous coat derived from peritoneum and this has an inner fibrous coat (Glisson's capsule) to which it is firmly adhered. The fibrous coat is of areolar tissue and follows the vessels and ducts to support them.(Dorland, 2012).

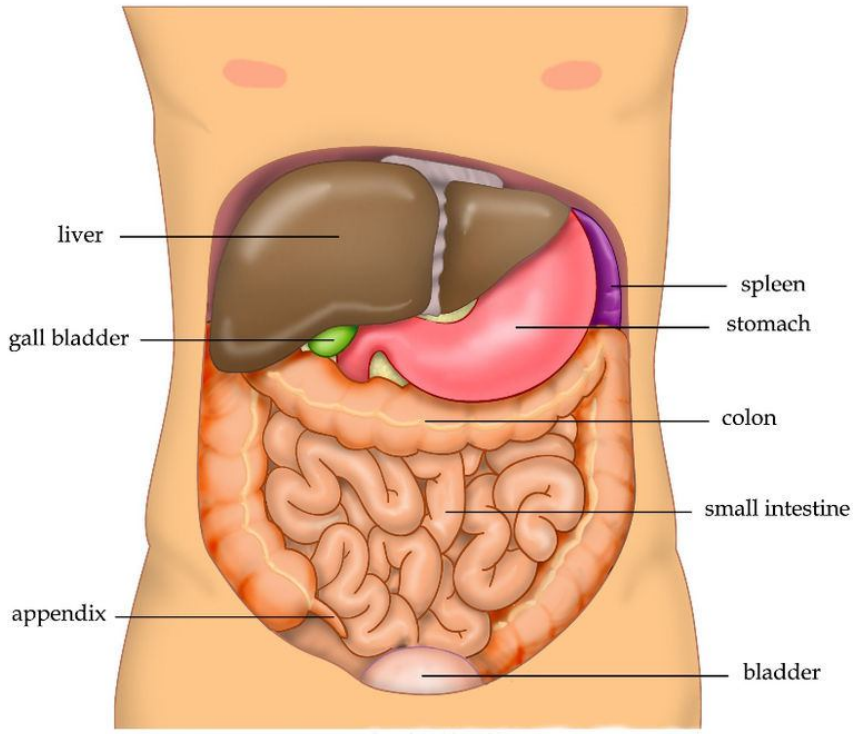

Figure (2.1): Shows human liver in abdomen. (www.wikipaedia.org)

2.1.1 Liver Gross Anatomy

2.1.1.1 Lobes

Gross anatomy traditionally divided the liver into two portions– a right and a left lobe, as viewed from the front (diaphragmatic) surface; but the underside (the visceral surface) shows it to be divided into four lobes and includes the caudate and quadrate lobes. (Vinay Kumar, 2015).

The falciform ligament, visible on the front of the liver, divides the liver into a left and a much larger right lobe. From the visceral surface, the two additional lobes are located between the right and left lobes, one in front of the other. A line can be imagined running from the left of the vena cava and all the way forward to divide

the liver and gallbladder into two halves. This line is called Cantlie's line.(Renz, 2014).

Other anatomical landmarks exist, such as the ligamentum venosum and the round ligament of the liver (ligamentum teres), which further divide the left side of the liver in two sections. An important anatomical landmark, the porta hepatis, also known as the transverse fissure of the liver, divides this left portion into four segments, which can be numbered starting at the caudate lobe as I in an anticlockwise manner. From this visceral view, seven segments can be seen, because the eighth segment is only visible in the parietal view. (Kuntz, 2009).

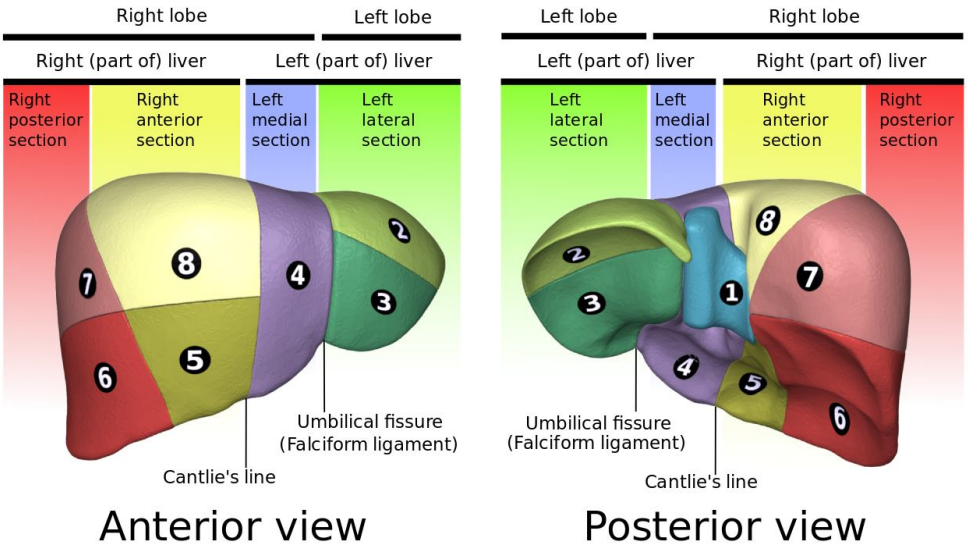

Figure (2.2): ShowsCouinaud classification system (www.wikipaedia.org)

2.1.1.2Surfaces

On the diaphragmatic surface, apart from a large triangular bare area where it connects to the diaphragm, the liver is covered by a thin double-layered membrane,

the peritoneum, that help reduces friction against other organs. *(*Singh, 2008).This surface covers the convex shape of the two lobes where it accommodates the shape of the diaphragm. The peritoneum folds back on itself to form the falciform ligament and the right and left triangular ligaments. *(*McMinn, 2003).These peritoneal ligaments are not related to the anatomic ligaments in joints, and the right and left triangular ligaments have no known functional importance, though they serve as surface landmarks. The falciform ligament functions to attach the liver to the posterior portion of the anterior body wall. (McMinn, 2003). The visceral surface or inferior surface, is uneven and concave. It is covered in peritoneum apart from where it attaches the gallbladder and the porta hepatis. *(*Singh, 2008).

2.1.1.3 Impressions

There are several impressions on the surface of the liver which accommodate the various adjacent structures and organs. Underneath the right lobe and to the right of the gallbladder fossa, are two impressions, one behind the other and separated by a ridge. The one in front is a shallow colic impression, formed by the hepatic flexure and the one behind is a deeper renal impression accommodating part of the right kidney and part of the suprarenal gland. *(*Skandalakis, 2009).The suprarenal impression is a small triangular depressed area on the liver. It is located close to the right of the fossa between the bare area and the caudate lobe and immediately above the renal impression. The greater part of the suprarenal impression is devoid of peritoneum and it lodges the right suprarenal gland.*(*Dorland,2011). Medial to the renal impression is a third and slightly marked impression, lying between it and the neck of the gall-bladder. This is caused by the descending

portion of the duodenum, and is known as the duodenal impression. *(*Dorland, 2011).

The inferior surface of the left lobe of the liver presents behind and to the left the gastric impression. This is moulded over the upper front surface of the stomach, and to the right of this is a rounded eminence, the tuber omentale, which fits into the concavity of the lesser curvature of the stomach and lies in front of the anterior layer of the lesser omentum.. (Dorland, 2011).

2.1.2 Functional Anatomy

The central area or hilum, known as the porta hepatis is where the common bile duct, hepatic portal vein, and the hepatic artery proper enter the liver. The duct, vein, and artery divide into left and right branches, and the areas of the liver supplied by these branches constitute the functional left and right lobes.The functional lobes are separated by the imaginary plane, Cantlie's line, joining the gallbladder fossa to the inferior vena cava. The plane separates the liver into the true right and left lobes. The middle hepatic vein also demarcates the true right and left lobes. The right lobe is further divided into an anterior and posterior segment by the right hepatic vein. The left lobe is divided into the medial and lateral segments by the left hepatic vein. (www.wikipaedia.org).

2.2 Liver function

The various functions of the liver are carried out by the liver cells or hepatocytes. The liver is thought to be responsible for up to 500 separate functions, usually in combination with other systems and organs. Currently, there is no artificial organ

or device capable of reproducing all the functions of the liver. Some functions can be carried out by liver dialysis, an experimental treatment for liver failure. (www.wikipaedia.org).

2.2.1 Blood supply

The liver receives a dual blood supply from the hepatic portal vein and hepatic arteries. The hepatic portal vein delivers approximately 75% of the liver's blood supply, and carries venous blood drained from the spleen, gastrointestinal tract, and its associated organs. The hepatic arteries supply arterial blood to the liver, accounting for the remaining quarter of its blood flow. Oxygen is provided from both sources; approximately half of the liver's oxygen demand is met by the hepatic portal vein, and half is met by the hepatic arteries.(Shneider, 2008).

Blood flows through the liver sinusoids and empties into the central vein of each lobule. The central veins coalesce into hepatic veins, which leave the liver and drain into the inferior vena cava. (Elaine N. Marieb, 2012*).*

2.2.2 Biliary flow

The biliary tract is derived from the branches of the bile ducts. The biliary tract, also known as the biliary tree, is the path by which bile is secreted by the liver then transported to the first part of the small intestine, the duodenum. The bile produced in the liver is collected in bile canaliculi, small grooves between the faces of adjacent hepatocytes. The canaliculi radiate to the edge of the liver lobule, where they merge to form bile ducts. Within the liver, these ducts are termed *intrahepatic* bile ducts, and once they exit the liver they are considered *extrahepatic*. The intrahepatic ducts eventually drain into the right and left hepatic ducts, which exit the liver at the transverse fissure, and merge to form the common hepatic duct. The

cystic duct from the gallbladder joins with the common hepatic duct to form the common bile duct.(Elaine N. Marieb, 2012).

Bile either drains directly into the duodenum via the common bile duct, or is temporarily stored in the gallbladder via the cystic duct. The common bile duct and the pancreatic duct enter the second part of the duodenum together at the hepatopancreatic ampulla, also known as the ampulla of Vater. (www.wikipaedia.org).

2.2.3 Synthesis

The liver plays a major role in carbohydrate, protein, amino acid, and lipid metabolism.

The liver performs several roles in carbohydrate metabolism: The liver synthesizes and stores approximately 100g of glycogen via glycogenesis, the formation of glycogen from glucose. When needed, the liver releases glucose into the blood by performing glycogenolysis, the breakdown of glycogen into glucose. The liver is also responsible for gluconeogenesis, which is the synthesis of glucose from certain amino acids, lactate or glycerol. Adipose and liver cells produce glycerol by breakdown of fat, which the liver uses for gluconeogenesis. (Elaine N. Marieb, 2012).

The liver is responsible for the mainstay of protein metabolism, synthesis as well as degradation. It is also responsible for a large part of amino acid synthesis. The liver plays a role in the production of clotting factors as well as red blood cell production. Some of the proteins synthesized by the liver include coagulation factorsI (fibrinogen), II (prothrombin), V, VII, VIII, IX, X, XI, XIII, as well as protein C, protein S and antithrombin. In the first trimester fetus, the liver is the

main site of red blood cell production. By the 32nd week of gestation, the bone marrow has almost completely taken over that task. The liver is a major site of production for thrombopoietin, a glycoprotein hormone that regulates the production of platelets by the bone marrow. *(*Jelkmann, 2001).

The liver plays several roles in lipid metabolism: it performs cholesterol synthesis, lipogenesis, the production of triglycerides, and a bulk of the body's lipoproteins are synthesized in the liver.(www.wikipaedia.com)

The liver plays a key role in digestion, as it produces and excretes bile (a yellowish liquid) required for emulsifying fats and help the absorption of vitamin K from the diet. Some of the bile drains directly into the duodenum, and some is stored in the gallbladder.(www.wikipadia.com)

The liver also produces insulin-like growth factor 1 (IGF-1), a polypeptideprotein hormone that plays an important role in childhood growth and continues to have anabolic effects in adults.(www.wikipaedia.org).

2.2.4 Breakdown

The liver is responsible for the breakdown of insulin and other hormones. The liver breaks down bilirubin via glucuronidation, facilitating its excretion into bile. The liver is responsible for the breakdown and excretion of many waste products. It plays a key role in breaking down or modifying toxic substances (e.g., methylation) and most medicinal products in a process called drug metabolism. This sometimes results in toxication, when the metabolite is more toxic than its precursor. Preferably, the toxins are conjugated to avail excretion in bile or urine. The liver breaks down ammonia into urea as part of the urea cycle, and the urea is excreted in the urine. (Elaine N. Marieb, 2012).

2.2.5 Other functions

The liver stores a multitude of substances, including glucose (in the form of glycogen), vitamin A (1–2 years' supply), vitamin D (1–4 months' supply), vitamin B12 (3–5 years' supply), vitamin K, iron, and copper.(www.wikipaedia.com).

The liver is responsible for immunological effects—the mononuclear phagocyte system of the liver contains many immunologically active cells, acting as a 'sieve' for antigens carried to it via the portal system.(www.wikipaedia.com).

The liver produces albumin, the most abundant protein in blood serum. It is essential in the maintenance of oncotic pressure, and acts as a transport for fatty acids and steroid hormones. (www.wikipaedia.com).

The liver synthesizes angiotensinogen, a hormone that is responsible for raising the blood pressure when activated by renin, an enzyme that is released when the kidney senses low blood pressure. (www.wikipaedia.org).

2.3 Ultrasound and Elastography:

Ultrasonography is a widely used medical imaging technique with many clinical applications. Used in clinical practice for more than 40 years, it is highly regarded for its ease of use, real-time capability, portability and low cost. Based on the propagation of mechanical waves and more particularly on high frequency compressional waves aka ultrasound, it allows the construction of morphological images of organs, but lacks a fundamental and quantitative information on tissue elastic properties; indeed the bulk modulus that governs the propagation of ultrasound is almost homogeneous in the different biological tissues and does not depend on tissue elasticity.(A. Sarvazyan, 1995).

Elastography, whose development started about 20 years ago, aims at imaging tissue stiffness, which provides an additional and clinically relevant information. Mapping the stiffness can either be estimated from the analysis of the strain in the tissue under a stress (quasi-static methods), or by the imaging of shear waves, mechanical waves, whose propagation is governed by the tissue stiffness rather than by its bulk modulus. (J. L.Gennisson, 2013).

Elastography techniques include transient elastography (FibroScan®), ARFI, Real Time Elastography, Shear Wave mode elastography and elasto-MR. Elastography can replace subjective palpation and is intended to image the mechanical properties of tissues and more particularly their stiffness. Tissue stiffness is described by the Young modulus expressed in kilopascals ($E = 3\gamma C^2$). The elastography methods are based on a common approach: measurement of deformation induced in a tissue by a force. (N. Frulio, 2013).

2.4Pathophysiology of liver stiffness

2.4.1Liver stiffness – definition

Going through the theory of elasticity is far beyond the scope of this review. However some basic notions are useful to better understand what stiffness means. From a physical and mechanical point of view, stiffness can be defined as the modulus of elasticity or Young's modulus (E). Hooke's law of elasticity is an approximation that states that the extension of a material is directly proportional to the applied stress, $\sigma = E\varepsilon$, where σ is the stress applied to the material, and ε is the strain induced in the material. Stiffness (E) is expressed in kilopascals (kPa) and represents the resistance of material to deformation. While stiff materials, such as

concrete, exhibit low strain even at high stress, soft materials such as biological soft tissues exhibit large strain even at low stress.(Sebastian Mueller, 2010).

LS, like any other soft tissue stiffness, depends on many factors. The first and main factor is the extracellular matrix of the organ. The extracellular matrix is a deformable structure that transfers the external forces through the liver. It can be compared to the foundation of a building. A second factor is the constraints that are applied on the organ. The more pressure that is applied to the liver at its boundaries, the stiffer it gets. A third factor is the internal pressure inside the organ – if blood, or another liquid is coming in and out, then stiffness will depend on the resistance that the organ applies to the flow. A fourth and important factor is the viscous effects which influence the time constant over which stiffness is tested. This effect is linked to frequency, ie, stiffness depends on frequency. While liver is soft at very low frequency (on the order of several hertz) which corresponds to manual palpation time-constant, it tends to be much harder at high frequencies (over several tens of kilohertz). (Sebastian Mueller, 2010).

2.4.2Measurement of liver stiffness using transient elastography (FibroScan)

The FibroScan (FS) (Echosens, Paris, France) device is the first elastography technique developed to quantitatively and noninvasively assess soft biological tissue stiffness *in vivo*. Liver was a natural first organ to study due to its size and rather homogenous texture. (Sandrin L, 2003).

Figure (2.3) : Shows FibroScan® machine (Sandrin L, 2003).

In principle, shear waves are generated through the liver and LS is deduced from their velocity. FS uses the technique called transient elastography (TE) or vibration-controlled transient elastography (VCTE™). It is based on the controlled generation of a transient shear wave using a servo-controlled vibration of known frequency and amplitude. LS is computed from the velocity of these mechanical waves using the following equation:

$$E=3\rho V\ 2\ s$$

where E is the Young's modulus or stiffness, ρ is the density, and V_s the shear velocity. The shear velocity measured by VCTE™ is a group velocity around 50 Hz. Minimum and maximum stiffness values that can be measured by FS are 1.5 kPa and 75.0 kPa respectively. (Sandrin L, 2003).

Technically, FS consists in a dedicated acquisition platform that includes a single channel ultrasound analog front end to emit and receive ultrasound signals, and a servo-controlled vibrator for the shear wave generation. The probe itself contains a sophisticated vibrator on the axis of which a single element ultrasound transducer is mounted. As shown, the vibration consists of a sinusoid period with a center frequency of 50 Hz. Its amplitude depends on the probe model: 2 mm peak-to-peak (PP) with the standard probe (model M), 1 mm PP with the pediatric probe (model S), and 3 mm PP with the obese patients dedicated probe (model XL). The shear wave propagation is monitored using ultrafast ultrasound acquisitions. (Sandrin L, 2003).

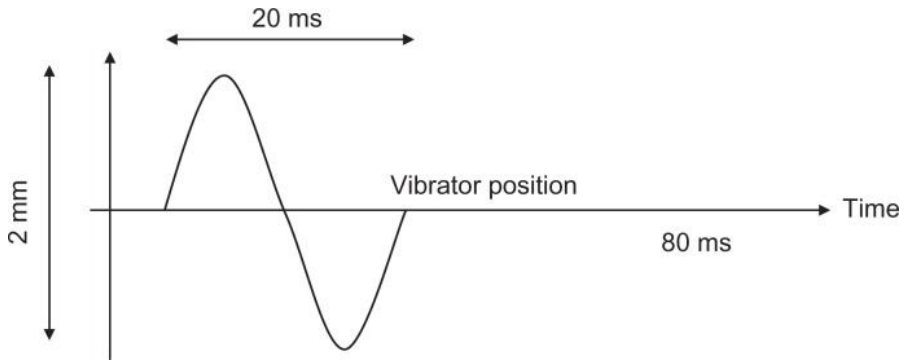

Figure (2.4) : ShowsFibroScan® vibration consists of a period with a center frequency of 50 Hz. The standard M probe has a 2 mm peak-to-peak amplitude.(Sandrin L, 2003).

In the standard examination procedures, LS measurements using FS are performed on the right lobe of the liver in intercostal position. This prevents direct compression of the liver that would eventually affect LS values. The patient is lying on his back with the right arm behind the head in order to enlarge intercostal space as much as possible. (Sandrin L, 2003).

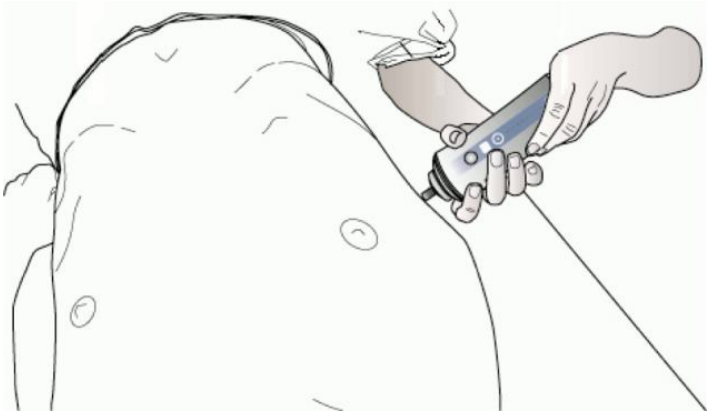

Figure (2.5) :Liver stiffness measurements are performed on the right lobe of the liver in intercostal position using FibroScan®.(Sandrin L, 2003).

The operator uses ultrasound M-mode and A-mode images(A & B) to locate the liver, and triggers the measurement by pushing on the probe button. The shear wave can be observed on the elastogram image (C) which represents the strains induced in the liver as a function of time and depth. It is computed from ultrasound data acquired at a very high frame rate during the shear wave propagation which lasts 80 ms.(Sandrin L, 2003).

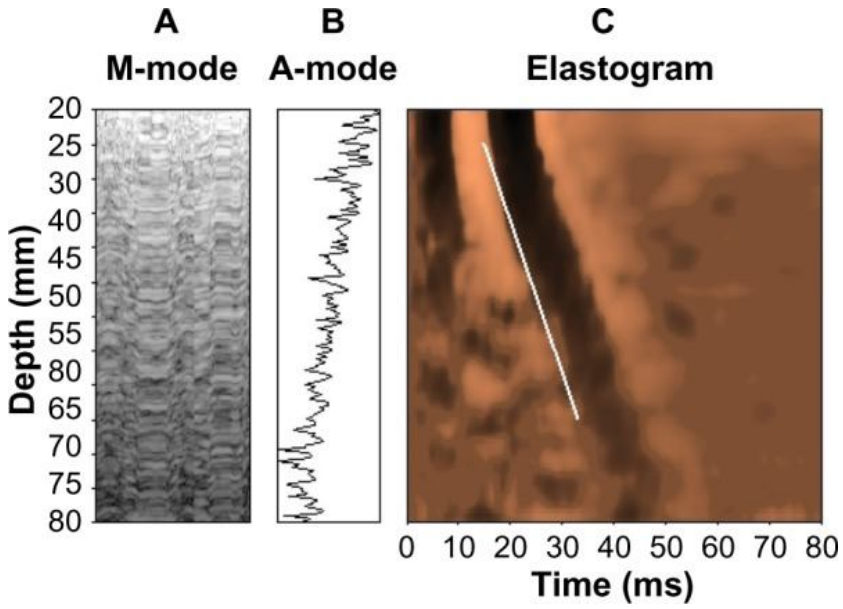

Figure (2.6): FibroScan® operator uses **A**) A-mode and **B**) M-mode images to locate the liver. The shear wave velocity is deduced from the **C**) elastogram which represents the strains induced in the liver by the shear wave propagation as a function of time and depth.(Sandrin L, 2003).

This scan is painless, takes less than ten minutes and produces immediate results. FibroScan has dramatically reduced the need for having a liver biopsy.FibroScan measures how quickly vibration waves pass through the liver. The more damaged or stiff the liver, the more rapidly the waves will pass through it. Results are presented as a number in kilopascals (kPa). A higher number indicates more liver damage.Results from FibroScan need to be interpreted based on other factors. However, a score of over 7.2 kPa indicates higher likelihood of significant fibrosis (F2 or greater on Metavir scale). A score over 14.5 kPa in someone with HCV/HIV coinfection indicates cirrhosis (F4 on the Metavir scale).The Metavir scale is used to score results from a biopsy.However, FibroScan it is very sensitive at picking up severe damage. It can therefore identify people who need HCV treatment more

urgently.If FibroScan results indicate serious liver damage, the test should be repeated. (http://i-base.info/guides/hepc/about-fibroscan).

2.5 Previous study

James Fung et al. (2013) had studied the normal liver stiffness range in a normal healthy Chinese population without liver disease. Of the 2,528 subjects, 1,998 were excluded with either abnormal liver parenchyma on ultrasound, chronic medical condition, abnormal blood tests including liver enzymes, fasting glucose, fasting cholesterol, high body mass index, high blood pressure, or invalid liver stiffness scan. The reference range for the 530 subjects without known liver disease was 2.3 to 5.9 kPa (mean 4.1, SD 0.89). The median liver stiffness was higher in males compared with females (4.3 vs 4.0 kPa respectively, $p<0.001$). There was also a decline in median Liver stiffness in the older age group, from 4.2 kPa in those <25 years to 3.4 kPa for those >55 years ($p=0.001$).

Das K et al. (2012) had studied the normal liver stiffness values in South Asian subjects. He found that LSM varies between 3.2 and 8.5 kPa in healthy subjects of South Asian origin.

CHAPTER THREE

MATERIALS AND METHODS

Chapter three

Materials and Methods

3.1 Materials

3.1.1 Study design

Descriptive, cross-sectional and analytical study.

3.1.2 Study area and Ultrasound machines used

The study was conducted in Khartoum state at Aliaa specialist hospital. LSM was performed using transient elastography (FibroScan® manufactured by Echosens (Paris, France)). By an experienced operator.

3.1.3 Sampling and sample size

Sample was number of 115 healthy Sudanese patients admitted for a fibroscan test. They are normal individuals aged between 5-66 years old, females are 33 and males are 82.

3.1.4 Inclusion criteria:

1. Non-alcoholic Sudanese patients.
2. Aged between 5-66 yrs.
3. Patients that performed an abdominal ultrasound and transient elastography (fibroscan).

3.1.5 Exclusion criteria:

1. Patients suffered from diabetes mellitus and hypertension.
2. Patients suffered from hepatitis B virus infection and hepatitis C virus infection.
3. Patients with heart dysfunction, liver dysfunction or metabolic syndrome.
4. Patients with abnormal liver parenchyma on ultrasound.
5. Patients with invalid liver stiffness scan.

3.2 Methods

3.2.1 Methodology and Sampling

Number of 115 fibroscan tests was performed for Sudanese patient aged between 5-66 years old. The age grouped to five groups as following ([5-18], [19-29], [30-40], [41-51],[52-66]), with commercially available Fibroscan machine.

3.2.2 Technique

LSM was performed with the subject lying in the supine position. The ultrasound probe is pressed against the skin (intercostal space) overlying the liver.

Using time-motion ultrasound image, measurements were obtained once a segment of the liver was located with a thickness of over 6 cm and free of large vascular structures. The probe generates a vibration and then measures the velocity of the resultant shear wave as it propagates through the liver. The aim is to obtain 10 successful measurements. The machine then calculates the median value of all the successful measurements (in kilopascals, kPa).

3.2.3 Data collection & Analysis:

Data was collected randomly and all statistical analysis was performed using Statistical Package for Social Sciences (SPSS).

3.2.4 Ethical Considerations:

The data was collected from the patients after their permission in addition to the radiology department and hepatic center permissions.

CHAPTER FOUR

RESULTS

Chapter four

Results

This study includes 115 Sudanese patients aged between 5-66 yrs. The age is grouped into five groups as following ([5-18], [19-92], [30-40], [41-51], [52-65]), with commercially available Fibroscan machine.The result after data analysis were:

Table (4.1): Shows age and the LSM statistical information for all patients

	Mean	**Median**	**STD**	**Min**	**Max**	**Std. Error Mean**
Age	39.71	39	13.36	5	65	1.246
E.med (kPa)	5.34	5.20	1.144	3.5	7.8	0.1067

Table (4.2): Shows frequency of male and female

Gender	**Frequency**	**Percentage**
Male	82	71.3%
Female	33	28.7%
Total	115	100%

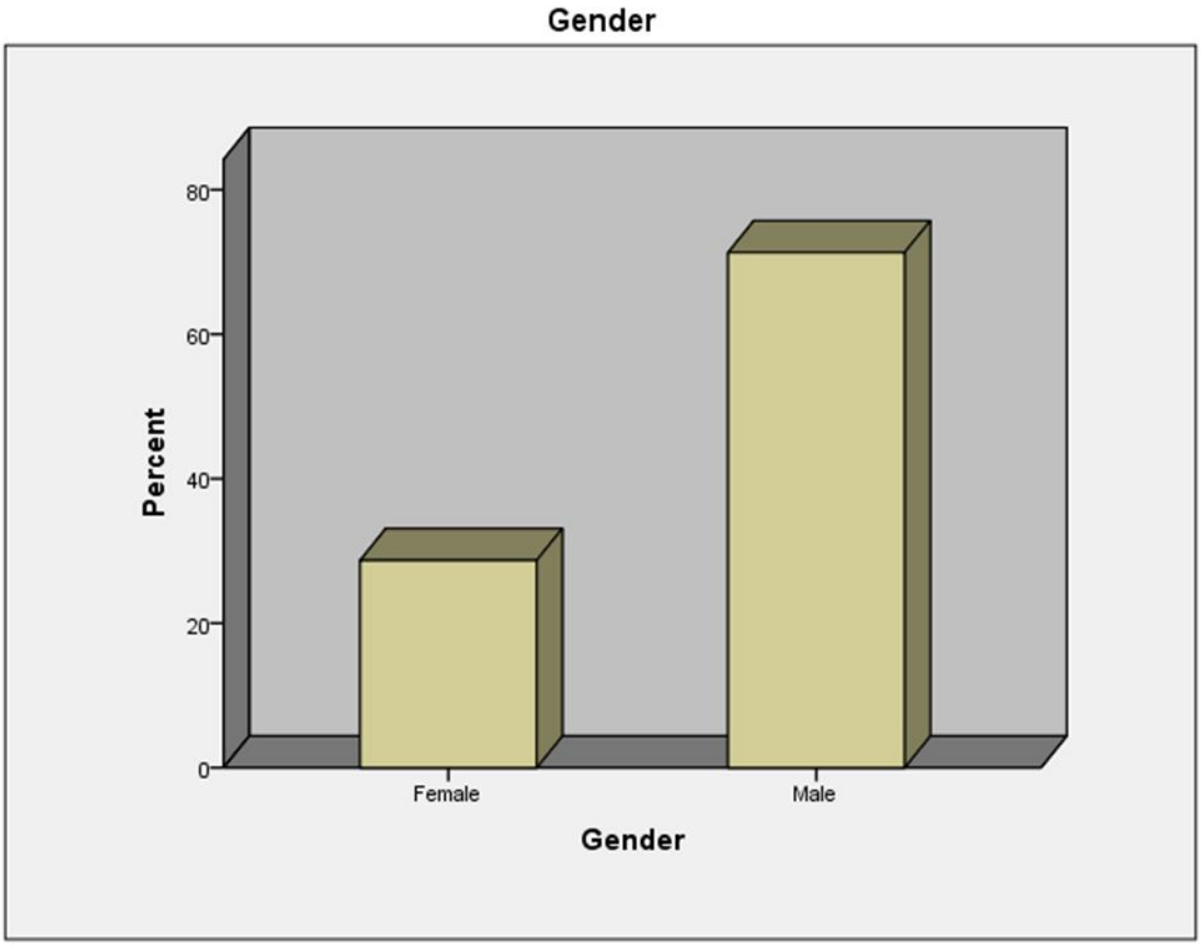

Figure (4.1): Shows distribution of males and females.

Table (4.3): Shows age and the LSM statistical information for males

	Mean	Median	STD	Min	Max	Quartile 3d
Age	39.71	38.50	13.106	5	65	49.00
E.med (kPa)	5.237	5.100	1.1188	3.5	7.7	6.100

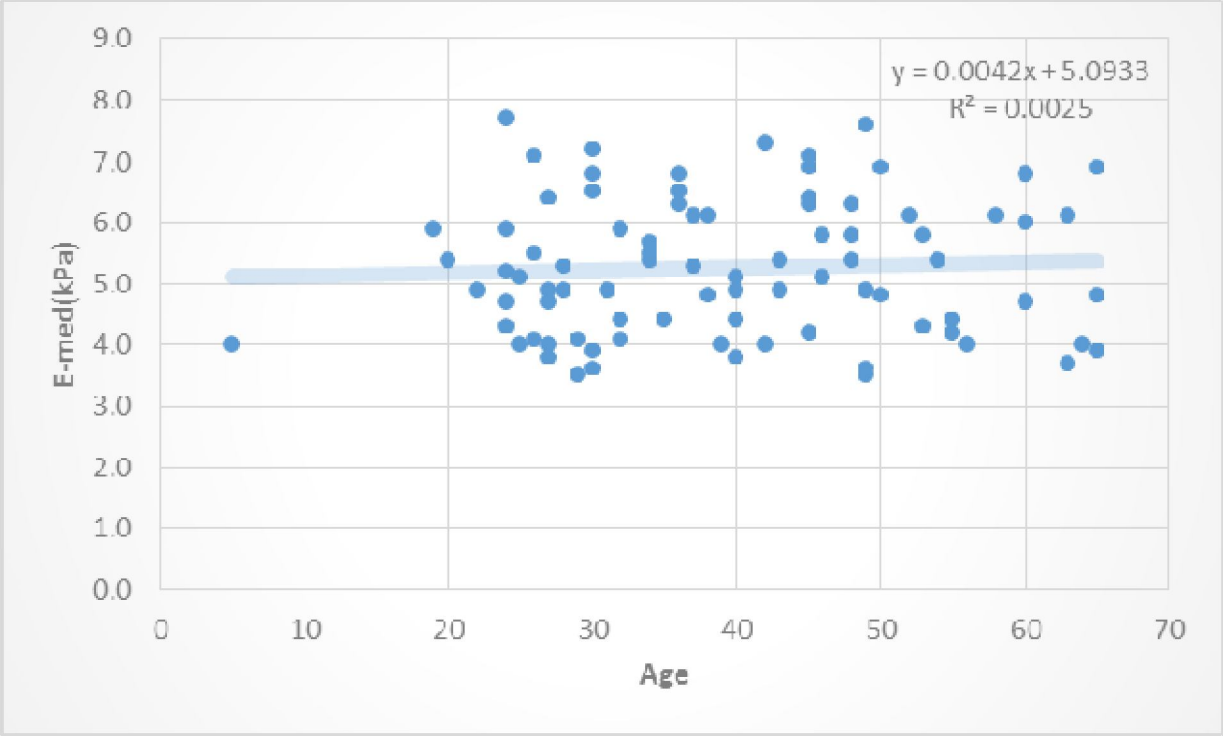

Figure (4.2): Shows distribution of main the median LSM for males.

Table (4.4): Shows age and the LSM statistical information for females

	Mean	Median	STD	Min	Max	Quartile 3d
Age	39.73	41.00	14.180	9	65	49.50
E.med (kPa)	5.588	5.400	1.1847	3.6	7.8	6.600

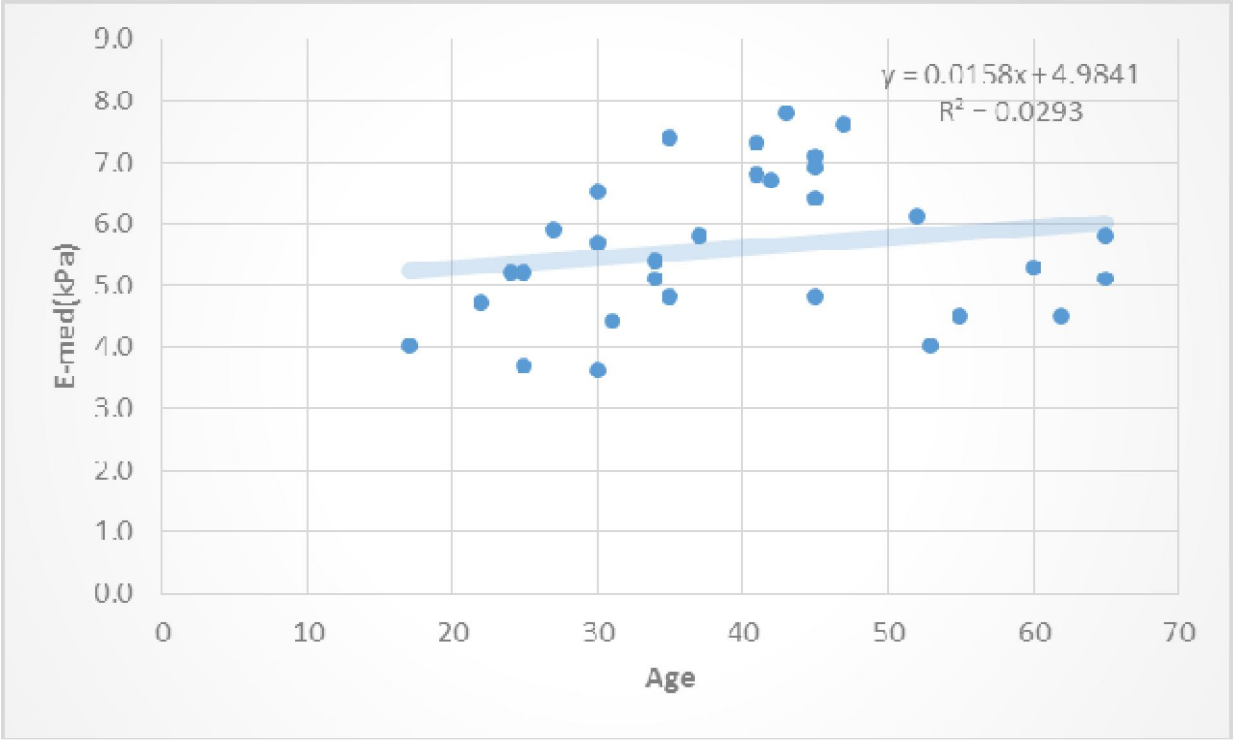

Figure (4.3): Shows distribution of the LSM for females.

Table (4.5): Shows frequency distribution of age groups

Age group (years)	Frequency
5-18	3
19-29	26
30-40	33
41-51	29
52-66	24
Total	115

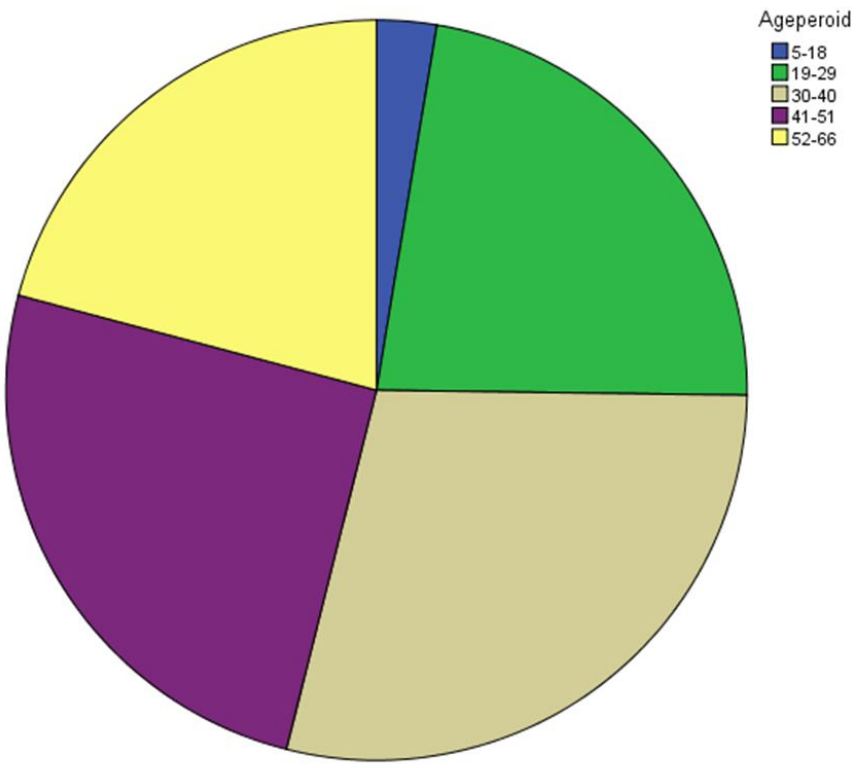

Figure (4.4): Shows frequency distribution of age groups.

Table (4.6): Show the LSM statistical information for age groups

Age group	Mean	Median	STD	Min	Max
(5-18)	4.667	4.000	1.1547	4.0	6.0
(19-29)	5.035	4.900	1.0284	3.5	7.7
(30-40)	5.291	5.300	1.0596	3.6	7.4
(41-51)	5.986	6.300	1.2589	3.5	7.8
(52-66)	5.029	4.750	0.9671	3.7	6.9

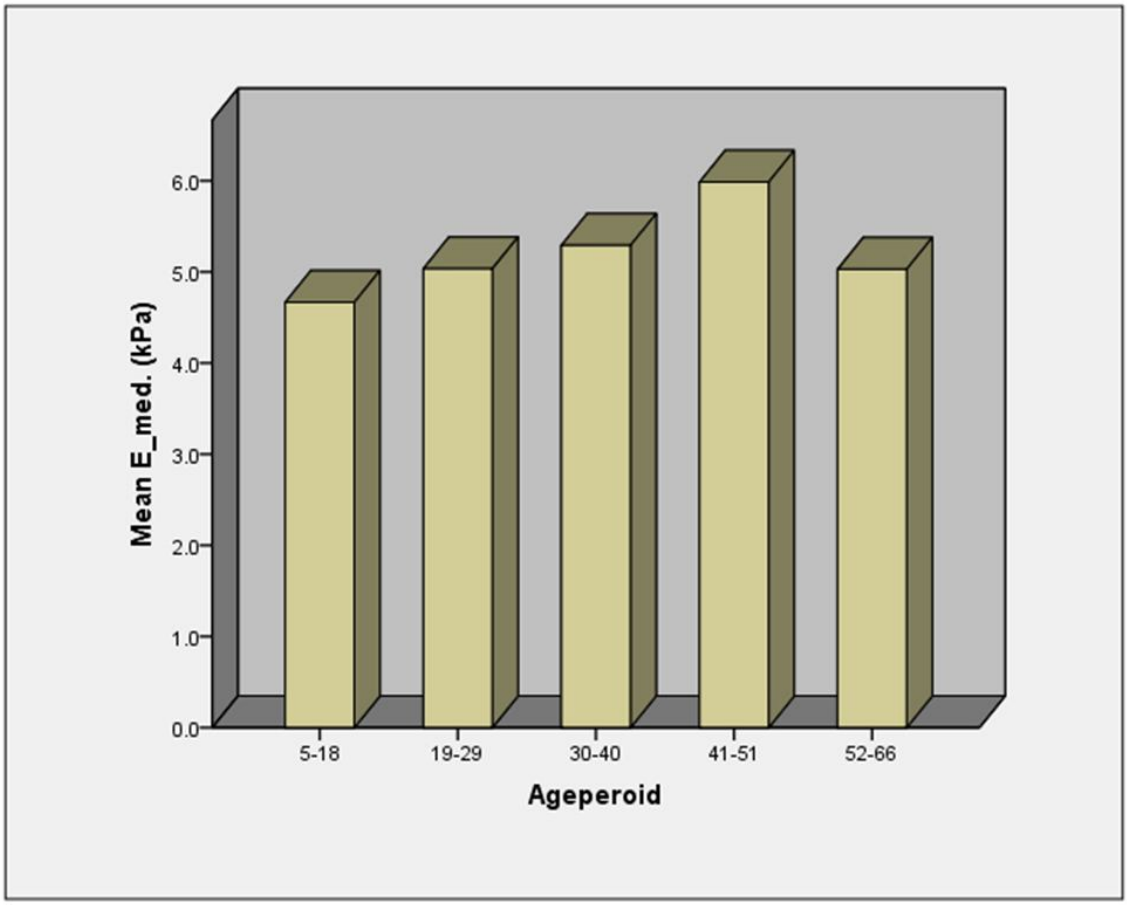

Figure (4.5): Show mean of LSM for all age groups.

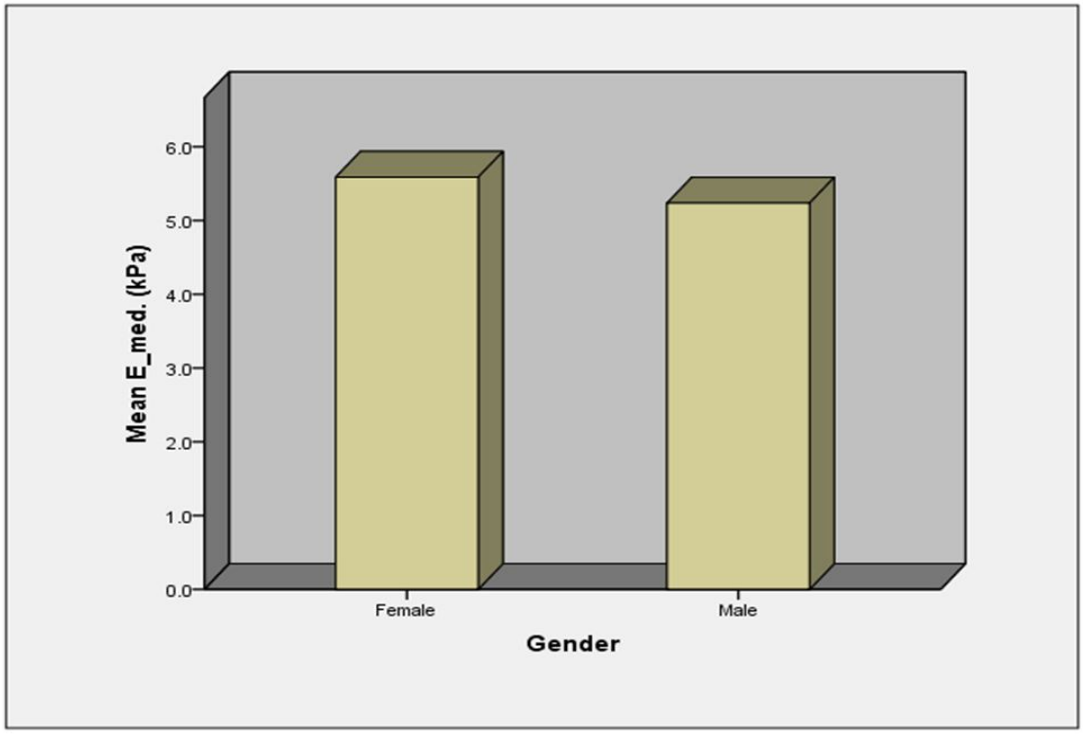

Figure (4.6): Show mean of LSM according to gender.

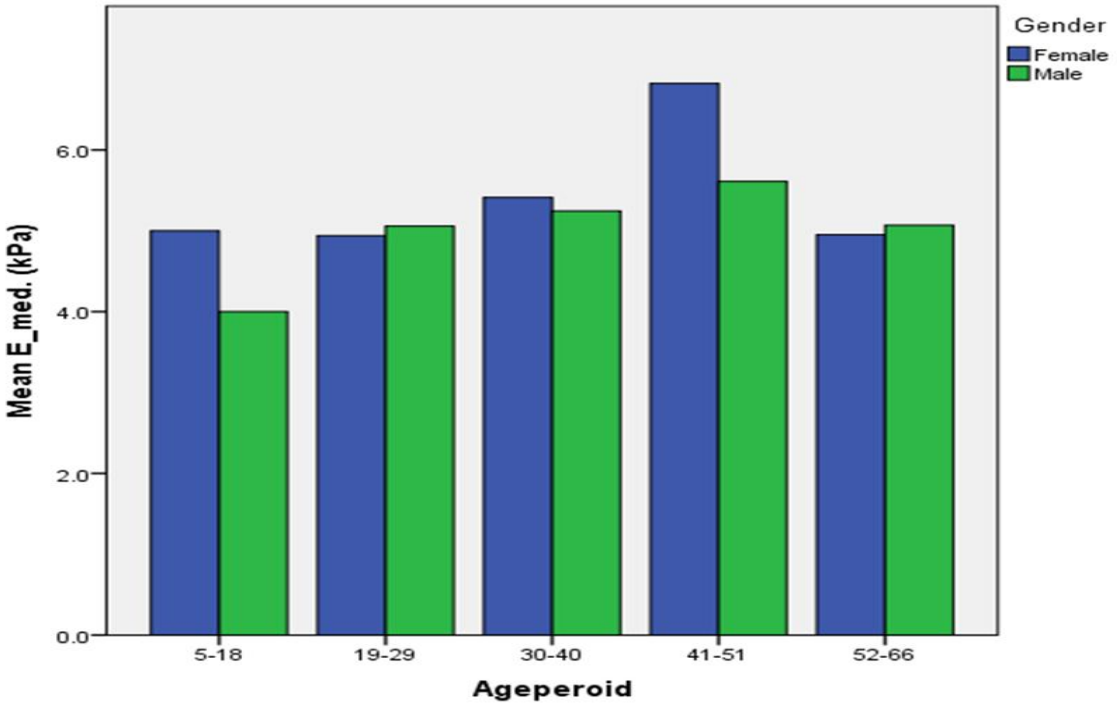

Figure (4.7): Show mean of LSM according to gender and age group.

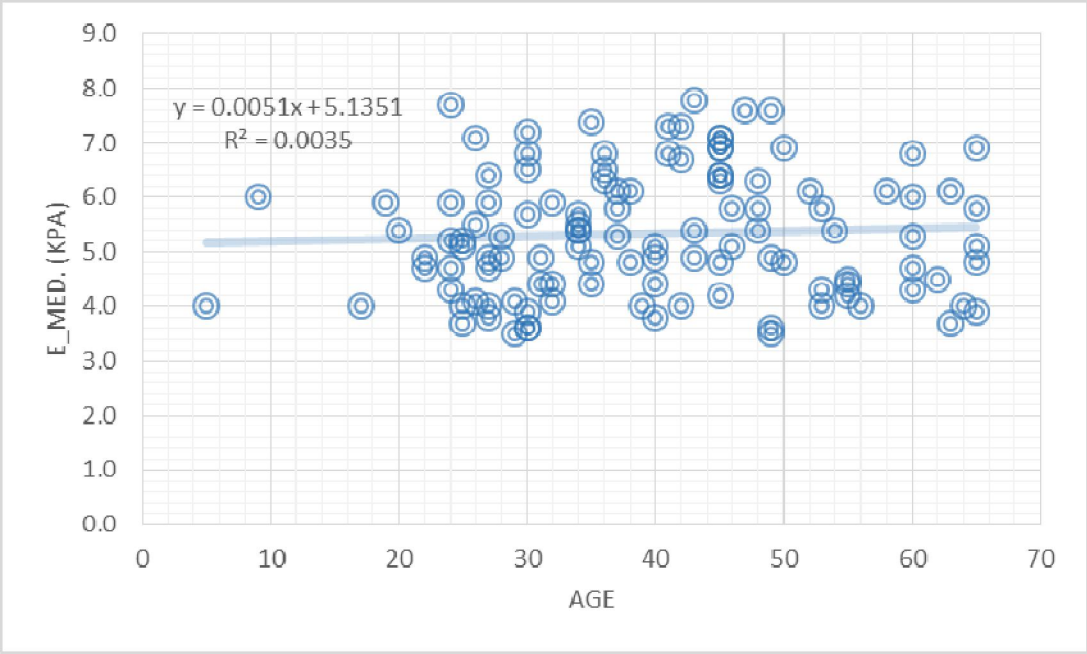

Figure (4.8): Show correlation between age and LSM.

CHAPTER FIVE

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

Chapter Five

Discussion, Conclusion and Recommendation

5.1 Discussion

This study includes 115 normal healthy Sudanese patients selecting those without ultrasonographic evidence of fatty liver, fibrosis and cirrhosis. In addition, non of these subjects were hepatitis B carriers. The study identified a healthy liver stiffness range from 3.5 to 7.8 kPa (mean 5.34, SD 1.14) in the Sudanese population.

The reference range is similar between males and females (3.5 to 7.7 kPa and 3.6 to 7.8 kPa respectively).

The mean of LSM was higher in females compared with males (5.58 vs 5.23 kPa respectively).

These results disagree with James F. (2013) who found that the normal range was 2.3 to 5.9 kPa (mean 4.11, SD 0.89) in Chinese subjects. The median liver stiffness was higher in males compared with females (4.3 vs 4.0 kPa respectively).

Also these results disagree with Das K (2012) who showed a reference range to be 3.2 and 8.5 kPa in South Asian subjects by calculating the 5th and 95th percentile respectively.

The study found that there was no significant correlation between age and LSM.

The mean of LSM for those with age (5-18), (19-29), (30-40), (41-51), (52-66) years was 4.6, 5.0, 5.2, 5.9, 5.0 kPa respectively. This means that the stiffness increase with age till 51 years and decline after that.

This result agree with James F. (2013) who found that there was decline in liver stiffness in ages more than 55 years.

These difference highlight the important fact that the liver stiffness values are not universal, and reference ranges should be derived for different population.

5.2 Conclusion

This study found that the range of normal liver stiffness in Sudanese population was between 3.5 to 7.8 kPa.

The overall mean of liver stiffness measurement in 115 Sudanese patients was [5.34 ±1.144] kPa.

There was no significant correlation between liver stiffness measurement and age.

Female gender was associated with higher liver stiffness values (mean 5.588, SD 1.1847) kPa compared with male gender (mean 5.237, SD 1.1188) kPa.

The study found that the mean liver stiffness increase gradually with age till 51 years old and decrease after that.

5.3Recommendations

- It is always important to know the reference value of the liver stiffness in Sudanese population, to state the pathology easily.
- Further studies should be done to correlate the LSM with body mass index, systolic and diastolic blood pressure and laboratory parameters .
- Further studies should be done using a larger sample size from different states of the country.
- The fibroscan test should done by an experienced operator.

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Appendix A:

Questionnaire

1- Age: …… years

2- Gender

☐ Male ☐ Female

3-Describe your life style

☐ Sedentary ☐ Active ☐ Moderate

4-Past history of hypertension

☐ Yes ☐ No ☐ I don't know

5-Past history of diabetes

☐ Yes ☐ No ☐ I don't know

6-Past medical problems

☐ Yes ☐ No ☐ I don't know

7-Taking any medications

☐ Yes specify ……..

☐ No

8- LSM

…….

Appendix B:

Fibroscan result