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6. Chapter six: Recommendation

Encourage about important for screen diabetic patient for NAFLD by send them for non invasive test (ultrasound) and confirm by CT to measure Hounsfield unit of fat or by MRI.

To minimize the burden of NAFLD among T2DM patients, First health education should be undertaken for all diabetic patients to improve dietary control and avoid excessive weight gain, exercise, stop smoking and drinking, and drug awareness that lead to fatty changes in liver.

5. Chapter five: Conclusion

NAFLD is a common chronic hepatic disorder globally.

NAFLD is a common association of DM patient observed in the current study demonstrates an alarming public health problem, it was more common among diabetic patient type 2.

NAFLD more in women than men.

NAFLD related to increase duration of diabetic.

Our result supports a role for routine ultrasound scan evaluation in T2DM to enhance clinical decision making and enable early recognition and management of NAFLD.

Lab test and ultrasound lack sensitivities and specificity, so best way to confirm it by biopsy. Or if not available doing CT or MRI to see fatty changes in liver.

4. Chapter four: Discussion

In the current study we found also duration of diabetic also correlated to occurrence of NAFLD ,this finding also supported by Belay Z et al(2017) in Southwest Ethiopia [19], *Patel H et al* (2018) in India [20] , so that duration of diabetic related to more duration of diabetic , more fatty changes.

Interestingly, this study provides further evidence that a normal serum ALT level provides little diagnostic or prognostic value when assessing patients for NAFLD, because more than four-fifths (86%) of our patients with NAFLD had normal ALT levels. Even when more stringent criteria were used (i.e., ALT_30 units/l in men and _19 units/l in women) [48], most patients with NAFLD (63%) had normal ALT levels. Therefore, serum ALT levels appear to be insensitive markers for NAFLD. Indeed, it is known that the full histological spectrum of NAFLD may be present among patients with normal liver enzymes [49].

It is evident that the level of liver enzymes will provide little diagnostic or prognostic value when assessing NAFLD patients. They appear to be insensitive markers for NAFLD [50].

Most patients with NAFLD are asymptomatic and typically are identified when abnormal liver studies are noted on routine laboratory assessment. In particular, the liver enzymes, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels are elevated. However, these enzymes may not be elevated in all cases of NAFLD, and the level of aminotransferase may not reliably predict the extent of inflammation and cirrhosis [51].

4. Chapter four: Discussion

This suggested a correlation between NAFLD and the various major risk factors commonly found in older people, such as obesity, DM, and dyslipidemia. Moreover, older patients are more likely to have advanced fibrosis, cirrhosis, and HCC when compared with middle-aged patients [39]

and also during this age group may also seek hospital due to related comorbidities that lead to increase prevalence among this age group.

Relation between age and sex in NAFLD patient, the present study found male more prevalence during age group 40-49 but then after that prevalence of female start to increase after age of fifty and reach more than male at age group 60-89, this finding support also by study conducted by Bandit et al (2017) in Thailand [40], and study by Eguchi et al in Japan (2012) [41].

This might be because NAFLD in men tends to occur earlier, especially in middle age (40–49 years) than in women (>50 years), which could lead to a male predominance in younger and middle-aged populations [42],

Accordingly, premenopausal women have a relatively low prevalence of NAFLD; however, the prevalence increases after the age of 50 years, peaks at 60–69 years[43][44] , After the age of 50 years, the protective effects of higher estrogen levels in women during pre-menopause are markedly eliminated in the transitional post-menopausal period [45][46] These associations between age and gender can be explained by natural changes in female physiology that increase the risk of insulin resistance , hyperlipidemia, and visceral fat accumulation, which are known as risk factors for the development of NAFLD[47].

4. Chapter four: Discussion

Although liver biopsy is the gold standard for the diagnosis of NAFLD, with a sensitivity of 100% and specificity of 90%, abdominal Ultrasonography is the most commonly used method [26][27].

According to table 2 for relation of sex and NAFLD ,While many studies have indicated that NAFLD is more common in men than women [28],[29],[30],[31], others have suggested the opposite [32],[33],[34] , Our study supported the findings of a higher NAFLD prevalence in females (60%) compare to prevalence of males (55%) , this may be due that most of females included in our study over-50-year,and most were likely post-menopausal. Although the prevalence of NAFLD tended to be higher in women for every age group, the largest difference was found among the 56–60-year-old age group. This suggests that sex hormones might play a role in NAFLD[35],[36], The fact that breast cancer patients treated with an estrogen receptor antagonist develop massive hepatic steatosis and even typical NASH indicates that estrogen affects development of this disease [37].

In the present study the prevalence rate of NAFLD was highest in the 60 – 69 years age group (34.5%) , the study conducted by in India by *Patel H et al* (2018) was more for age group (50 – 59) 37% [20], while study Farrell et al (2013) in Chinese the prevalence was also more for age group (60 – 69) [38], which support our finding , this may be due that the diagnosis of NAFLD requires high index of suspicion, particularly in obese patient over the age of 45 years with history of diabetes mellitus[20] , but the age distribution of NAFLD might change in the future as rates of obesity in young people continue to increase in most countries[38].

3. Chapter four: Discussion

Non-alcoholic fatty liver disease is the most serious liver disorder and cause of cirrhosis among diabetic patients [16][17][18].

Setting the objective of evaluating the occurrence of NAFLD and associated factors in type 2-Diabetic patients attending AL-Imamain AI-Kadhimiyain teaching hospital, we evaluated 50 diabetic patients who fulfilled the inclusion criteria.

In the present study the result of prevalence of NAFLD was 58% including both DM1 and DM2 while some studies take only DM2 and *prevalence was 73%* Southwest Ethiopia [19] by Belay Z. *et al(2017)* , in India 64% [20] by *Patel H et al* (2018) , the other study take only DM1 and prevalence was Italy 24%[21] by Gaiani et al (2009) France 4% [22] by Petit et al (2015) , Iraq 10% by Farhan R al (2018)[23]

This discrepancy in the percentage between our study and other countries may be due that: use of ultrasound and serum enzymes as the sole marker of NAFLD is another limitation as both modalities are not the most sensitive, specific and predictive method for detecting (quantifying) liver as ultrasound is operator dependent fat despite being cheap and accessible in developing countries, The computerized tomography (CT) scan and magnetic resonance imaging (MRI), although more sensitive in detecting minimal levels of hepatic steatosis, are expensive and impractical as screening tools[24,25] and some radiologist prefers not to document fatty in unless patient converted to second stage on ultrasound, and also we find 5 patient that have elevated lipid profile and liver enzyme but still appear normal on ultrasound as they may be at first stage of ultrasound and not documented by radiologist, it may be also due size of the study population is limited patient number compared to other samples.

4. Chapter three: Results

this figure will show relation between age and sex in distribution of NAFLD that during 40-49 more male when age increase the female number increase reaching more than male at age 60-89.

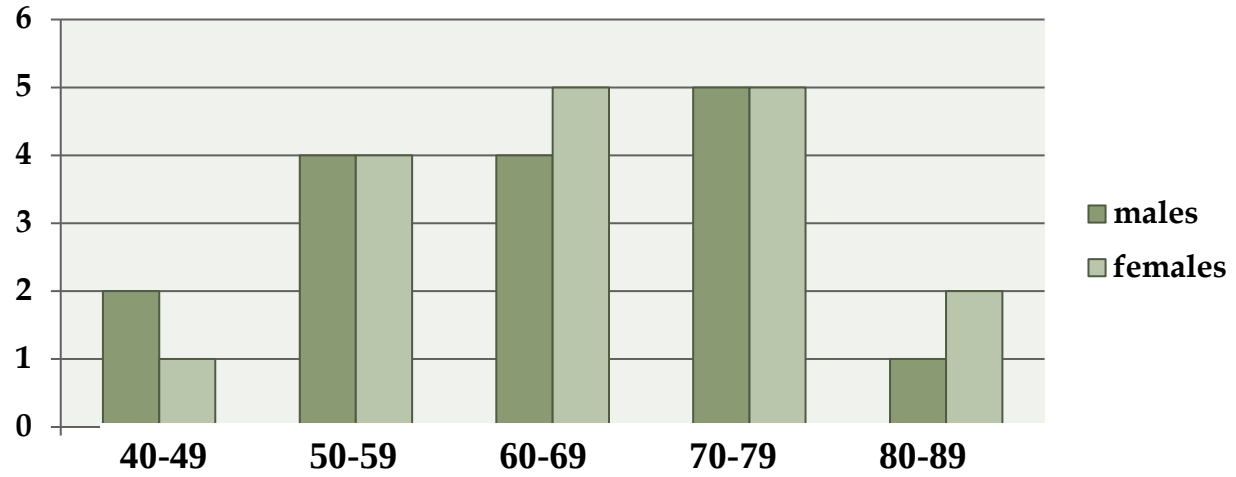


Figure 3: relation between age and sex in distribution of NAFLD in DM patients.

the figure below design to see relation between duration of diabetic mellitus and occurrence of NAFLD, as we see at duration less than 5 years negative lab more but that start to become more at duration more than 10-15 years.

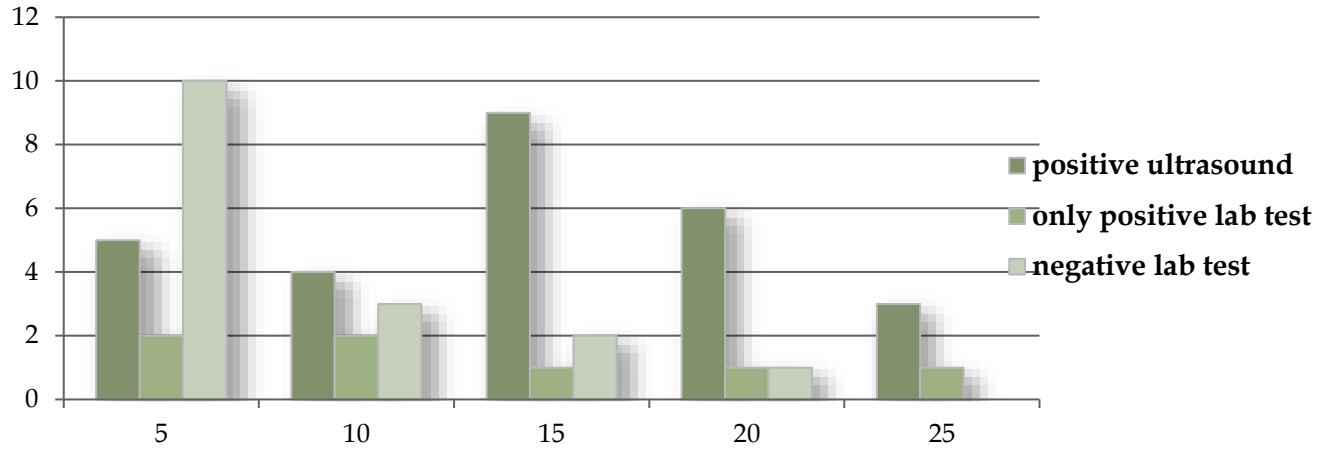


Figure 4: relation between duration of diabetic mellitus and occurrence of NAFLD.

3. Chapter three: Results

the table below had been design to see distribution of NAFLD case according to age, we found more age group in NAFLD was from 60-69 followed by 50-59 , then from 70-89 ,and there was no case of NAFLD in age less than 40.

Age	Case N	NAFLD	NON –NAFLD
20 -29	4 (8%)	_	4 (19.0%)
30 -39	2 (4%)	_	2(9.5%)
40 -49	3 (6%)	2 (6.9%)	1 (4.8%)
50 -59	14 (28%)	8 (27.6%)	6 (28.6%)
60 -69	13 (26%)	10 (34.5%)	3 (14.3%)
70 -79	9 (18%)	5 (17.2%)	4 (19.0%)
80 -89	5 (10%)	4 (13.8%)	1 (4.8%)

Table 2: relation between age and NAFLD in DM patients.

3. Chapter three: Results

this table had been design to show relation between NAFLD in diabetic mellitus patient and gander, as we see that female 18(60%) more than male 11(55%)

Sex	NAFLD	NON- NAFLD	Total
Male	11 (55%)	9 (45%)	20
Female	18 (60%)	12 (40%)	30
	29 (58%)	21 (42%)	50

Table 1: Relationship between sex and NAFLD in DM patients.

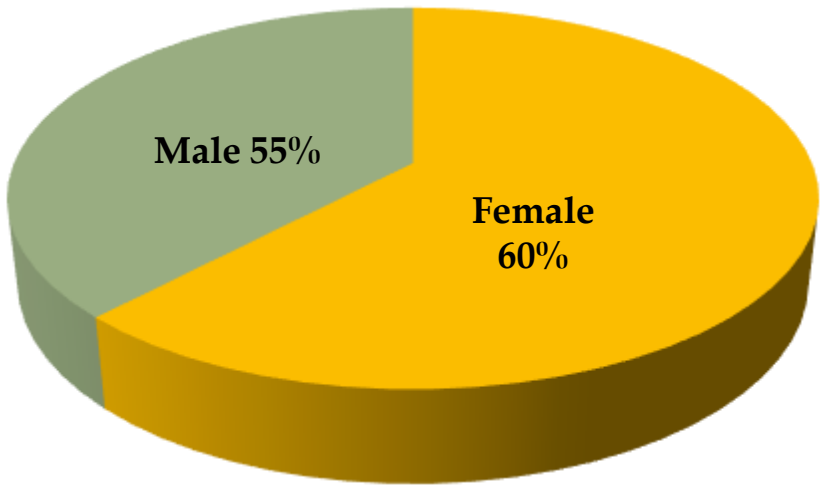


Figure 2: sex ratio in NAFLD in DM patients.

3. Chapter three: Results

This study had included 50 diabetic mellitus patients, including both diabetic mellitus type1 and type2 , Ranging between 20-89 years.

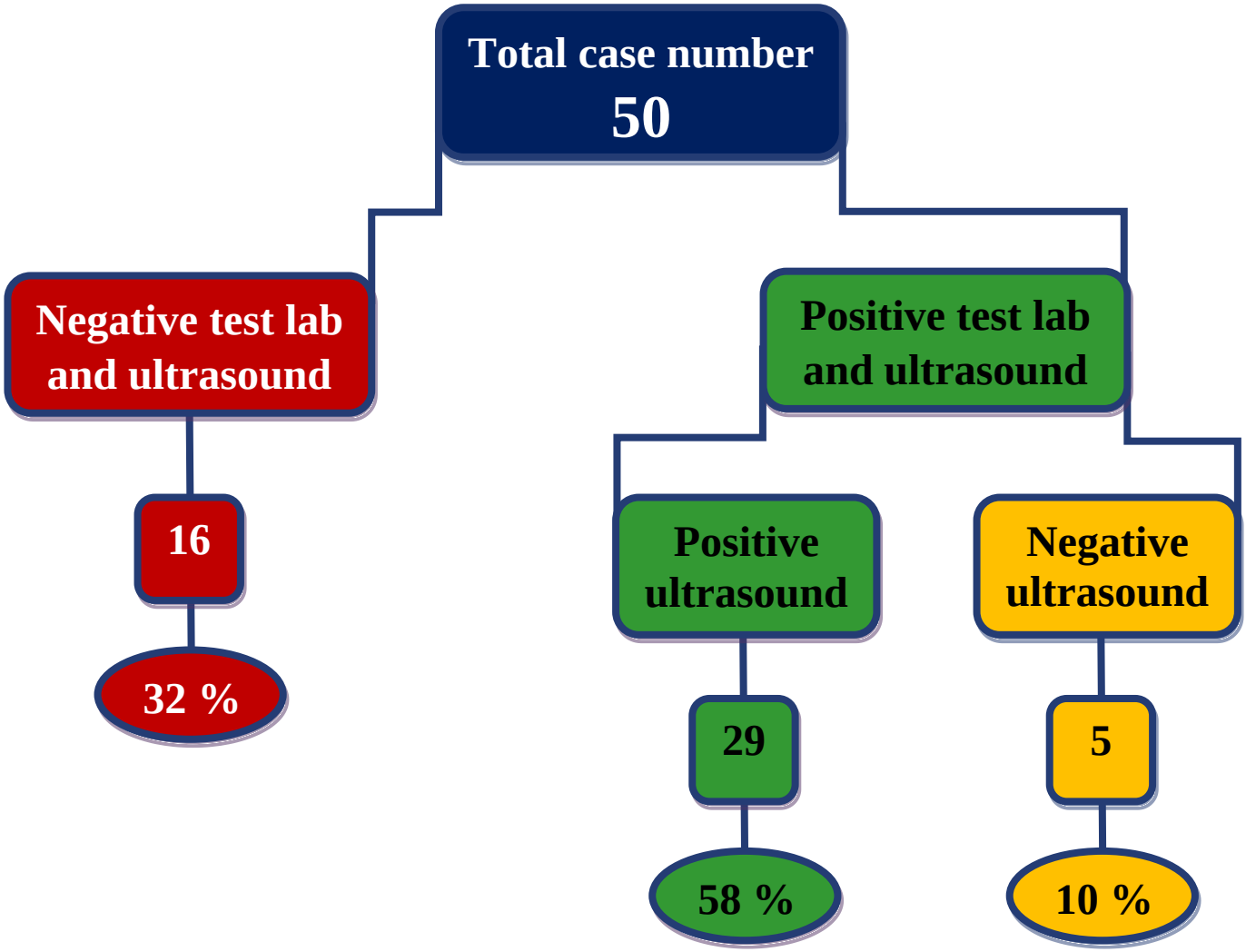


Figure 1: distribution of cases numbers that have fatty liver from non fatty in diabetic patients .

according to this figure we find in current study that the prevalence of fatty liver in diabetic patient was 58% , and 32% of patient doesn't have fatty liver , but there was 10% of patient have positive lab test but ultrasound finding was negative.

2. Chapter two: Patients and methods

Study design:

Cross section study up on diabetic patient attending AL-Imamain AI-Kadhimiyain teaching hospital during the period from October 2018 – February 2019.

Patient sample:

The sampling method was a random taken of 50 diabetic patient attending the inpatient department of medicine from age 20 t0 80 involve 30 case female and 20 case male . and patient to be included in our study should be diabetic and without history of chronic liver disease or take medication that elevate liver enzyme .

Exclusion criteria:

1- alcoholic intake.
2- chronic liver disease of any cause.
3- intake of hepatotoxic drug.
4- history of viral hepatitis.
5- pregnancy.
6- recent gastrointestinal surgery .

Study instrument:

A questionnaire had been design by researcher and supervisors were made for best acceptable form for process of data collection.

Data collection:

Our study was on take diabetic patient from medicine wards after exclusion criteria and ask them about baseline data collection include patient sex , age , duration of the diabetes , residency , type of diabetic mellitus then send them for lipid profile{{(total cholesterol (TC), serum triglycerides (TG),low density lipoprotein (LDH), high density lipoprotein (HDL)}} , liver enzyme {{ aspartate aminotransferase (AST), alanine aminotransferase (ALT) }} and ultrasound.
This investigation was done in hospital lab and recorded in patient case sheet.

1. Chapter one

1.8- Aim of study .

The aim from this study to estimate prevalence of fatty liver changes in diabetic patient.

1.7.3. Liver biopsy

Liver biopsy is the gold standard for diagnosis of NAFLD. It provides both diagnostic and prognostic information by assessing the presence of hepatocyte injury and fibrosis or cirrhosis [16].

Histological findings in NASH include:

- **Steatosis: Fat droplets (triglyceride) within hepatocytes can be large, displacing cellular contents to the periphery, small, or a mix of both types.**
- **Inflammation: Mixed neutrophilic and mononuclear cell infiltrates are present within the lobule; portal chronic inflammation can occur, especially in children and after treatment, but is uncommon; ballooning enlargement of hepatocytes with rarefication of cytoplasmic contents is a marker of hepatocyte injury.**
- **Mallory-Denk bodies: These eosinophilic cytoplasmic aggregates of keratins are typically smaller than those seen in alcoholic hepatitis and are usually found in ballooned hepatocytes.**
- **Glycogen nuclei: These clear intranuclear vacuoles fill the nucleus.**
- **Fibrosis: Similar to that seen in alcoholic liver disease, with perivenular deposition around the central vein and a "chicken wire" pattern of sinusoidal fibrosis; it signifies a risk for progression to end-stage liver disease.**

Fibrosis is staged as:

1. **Per sinusoidal or periportal only**
2. **Per sinusoidal and periportal**
3. **Bridging**
4. **Cirrhosis**

1.7.2. Imaging

Computerized tomography :-

Contrast-unenhanced Computerized tomography (CT) is the most accurate CT technique used to detect and characterize hepatic steatosis.
The CT diagnosis of hepatic steatosis is made by measuring the difference in liver and spleen attenuation values in Hounsfield units.
In individuals without hepatic steatosis, the mean attenuation value for the liver is at least 4 Hounsfield units greater than for the spleen[14], however, in subjects with hepatic steatosis, the mean attenuation value for the liver is lower than that for the spleen, so the liver appears darker than the spleen, rather than brighter. This lower attenuation of the liver in hepatic steatosis is thought to be secondary to the accumulation of lipids (triglycerides and cholesterol) within the hepatocyte [15].

Magnetic resonance image :-

MRI is sensitive noninvasive approach to detecting liver fat. Phase shifting can be useful for identifying focal fat based on its loss of intensity onT1-weighted images [11].
Fat deposition also can be diagnosed by observing the signal intensity loss of liver on MRI after the application of chemical fat saturations equences, but this method is less sensitive than is chemical shift imaging for the detection of fatty liver.
Chemical shift gradient-echo (GRE) imaging with in-phase and opposed-phase acquisitions is the most widely used MR imaging technique forthe assessment of fatty liver. The signal intensity of the normal liver parenchyma is similar on inphase and opposed-phase images.

1.7.2. Imaging

Ultrasonography:-

Varies depending on the amount of fat and whether deposits are diffuse or focal.

Diffuse steatosis may appear as follows:

• Mild—Minimal diffuse increase in hepatic echogenicity with normal visualization of diaphragm and intrahepatic vessel borders

• Moderate—moderate diffuse increase in hepatic echogenicity with slightly impaired visualization of intrahepatic vessels and diaphragm

• Severe—Marked increase in echogenicity with poor penetration of posterior segment of right lobe of liver and poor or no visualization of hepatic vessels and diaphragm

Focal fatty infiltration and focal fatty sparing may mimic neoplastic involvement. In focal fatty infiltration, regions of increased echogenicity are present within a background of normal liver parenchyma [13].

1. Chapter one: Introduction

1.6- Diagnosis of NAFLD.

The diagnosis of NAFLD divided into:

1- Lab test

2- Imaging (Ultrasonography ,CT and MRI)

3- Liver biopsy

1.7.1. Lab test

Normal liver tests are common in patients with NAFLD.
The AST/ALT ratio can be helpful in distinguishing alcoholic hepatitis from NAFLD or NASH as AST/ALT ratio >2 suggests alcoholic hepatitis, whereas patients with NASH typically have ALT levels that exceed AST levels in the absence of cirrhosis; AST is typically greater than ALT in NASH with cirrhosis[11].
Alcoholic hepatitis AST > ALT, typically >2 to 1 ratio
Nonalcoholic steatohepatitis ALT > AST, sometimes >2 to 1 ratio

Tests for liver synthetic function, such as the prothrombin time and serum albumin level, will be normal unless there is development of cirrhosis.
Exclusion of other liver disease is important. Chronic hepatitis B (HBV) and HCV infection should be ruled out. Other reasonable tests to order include serum iron studies, antinuclear antibodies, antismooth muscle antibodies, antimitochondrial antibodies, α-1 antitrypsin levels, and serum ceruloplasmin.
Substantial alcohol use can be assessed by laboratory testing if the information gathered through history alone is questionable. Random serum alcohol tests may be considered.
A ratio of desialylated transferrin to total transferrin greater than 0.013 has an 81% sensitivity and 98% specificity in diagnosing current alcohol use,25 depending on amount of alcohol intake [12].

1. Chapter one: Introduction

1.6- Risk factor of NAFLD. [10]

Established risk factors:

- Obesity
- Type 2 diabetic mellitus
- Hypertriglycemia
- Metabolic syndrome

Suspected risk factors:

- Hypothyroidism
- Hypopituitarism
- Hypogonadism
- Obstructive sleep apnea
- Polycystic ovarian syndrome
- Total parenteral nutrition
- Rapid weight loss (e.g. following gastric bypass surgery)
- Sedentary lifestyle

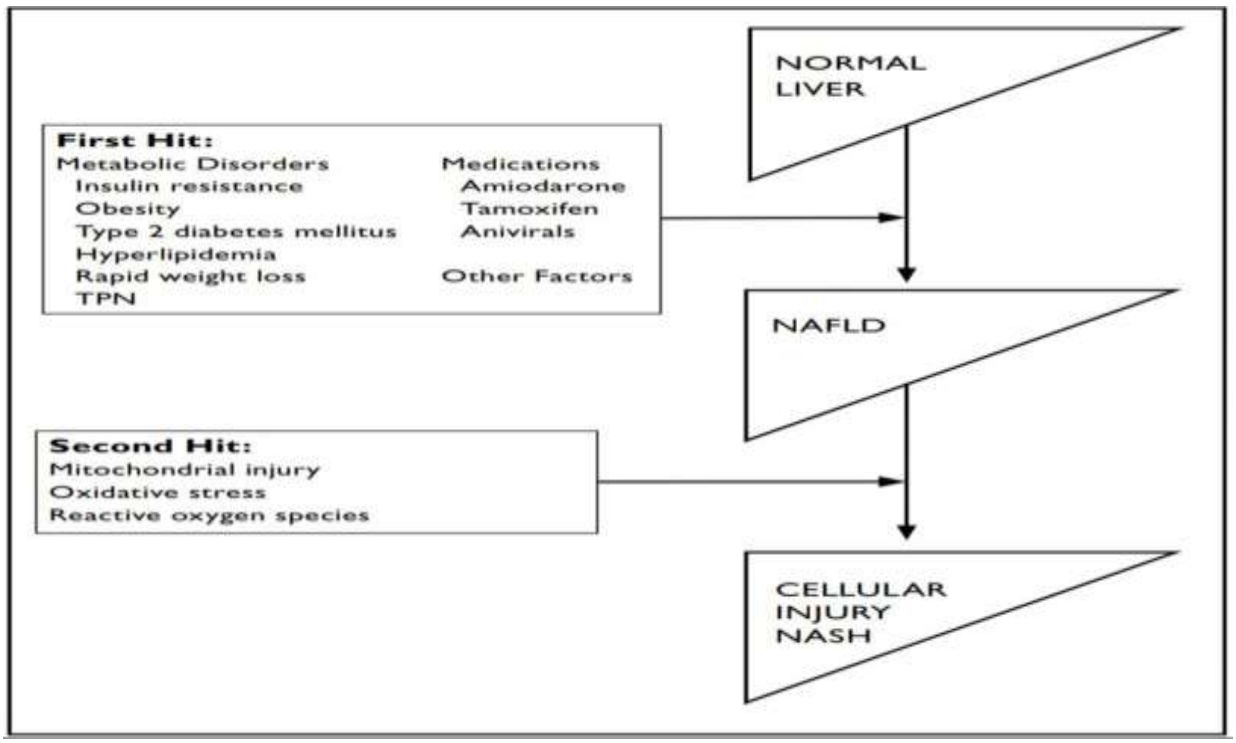
1. Chapter one: Introduction

1.5- Pathogenesis of NAFLD .

Despite recent research, the precise pathophysiologic mechanisms that result in NAFLD remain unknown.

However, a "two hit" theory implicates both insulin resistance fibrosis and cirrhosis Fatty acid accumulation in the liver (the "first hit") may occur secondary to an imbalance between fatty acid delivery to and export from the liver. As fatty acid retention increases, steatosis develops.

The mechanism by which steatosis progresses to steatohepatitis, and subsequently to fibrosis is unclear, but oxidative stress has been proposed as the "second hit." Mitochondrial injury, leading to ATP depletion, reactive oxygen species generation, lipid peroxidation, and cytokine induction may mediate hepatocyte injury [9].



1. Chapter one: Introduction

1.4- Classification of NAFLD. [8]

CLASS 1: Only steatosis

CLASS 2: Steatosis + non specific lobular inflammation NASH

(Non alcoholic Steatohepatitis)

CLASS 3: Steatosis + Inflammation +ballooning hepatocyte

CLASS 4: class 3 + Fibrosis/Mallory Denk bodies.

1. Chapter one: Introduction

1.3- Relation between NAFLD and DM.

Insulin resistance is the pathophysiological hallmark of nonalcoholic fatty liver disease (NAFLD), one of the most common causes of chronic liver disease in Western countries, The mechanisms underlying the development of inflammatory change and later fibrosis in relation to hepatic steatosis are uncertain, but insulin resistance probably plays a role as it is now considered to be an intrinsic defect in NAFLD [3].

The most plausible mechanism is that Insulin resistance in adipose tissue results in accelerated lipolysis, causing an increased flow of free fatty acids to the liver, thus favouring hepatic fat accumulation. The distribution of adipose tissue is also important since it has been shown that visceral adipose tissue is more insulin resistant than subcutaneous adipose tissue. Consequently visceral adipose tissue by increased portal free fatty acid flow to the liver seems to be an important regulator of fatty liver [4]. Insulin resistance and compensatory hyperinsulinemia are also related to increased *de novo* lipogenesis (synthesis of free fatty acids in the liver) which is another contributor to hepatic fat accumulation, and the generation of oxidative stress by way of reactive oxygen species and an ability to worsen steatosis by way of up-regulation of sterol regulatory element-binding protein [5]. Moreover, insulin resistance and Hyperinsulinemia can stimulate fibrogenesis by way of up-regulation of connective tissue growth factor and direct interactions with hepatocellular carcinoma, effects that are particularly marked in the presence of hyperglycemia [6], These finding may explain why patients who have type 2 diabetes and NASH have rapidly progressive disease and a poor prognosis [7].

1. Chapter one: Introduction

1.1 Definition of NAFLD.

Non alcoholic fatty liver disease (NAFLD) is the commonest cause of liver dysfunction in the Western world and comprises a clinical spectrum from steatosis (triacylglycerol [TAG] infiltration in >5% of hepatocytes),fatty infiltration plus inflammation, and hepatocellular ballooning degeneration (non alcoholic steatohepatitis[NASH]), to fibrosis and ultimately cirrhosis, in the absence of excessive alcohol consumption (a typical threshold being <30 g per day for men and <20 g per day for women) [1].

1.2 History of discovery NAFLD .

July 1980, Jurgen Ludwig and colleagues at Mayo Clinic in Rochester, Minnesota, published the first article to identify non-alcoholic steatohepatitis (NASH). At the time, steatohepatitis an inflammation of the liver that is accompanied by the aberrant accumulation of fat was thought to be caused by excessive alcohol consumption.

But the Mayo study described 20 people with fatty and inflamed livers none of whom was a heavy drinker.

Most had some liver scarring, also known as fibrosis. Three of the patients had cirrhosis, liver damage that results from such scarring. The study also noted that "most patients were moderately obese, and many had obesity associated diseases."Although now regarded as a landmark study, the Mayo article had little impact at first. Throughout the 1980s and 1990s, however, researchers at Mayo Clinic, as well as a small number of other liver specialists such as Oliver James and Christopher Day at Newcastle University, UK, discuss that non-alcoholic fatty liver disease (NAFLD), of which NASH represents a moderately advanced stage, which was serious condition. Doctors came round to the importance of NAFLD especially as they encountered greater numbers of people with advanced liver disease who were neither alcoholic nor affected by viral hepatitis[2].

Abstract

Background: Worldwide, Non-alcoholic fatty liver disease has become an important cause of chronic liver disease.

NAFLD represents a spectrum of liver injury ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) which may progress to advanced fibrosis and cirrhosis.

Insulin resistance is the pathophysiological hallmark of nonalcoholic fatty liver disease.

Aim: To estimate prevalence of fatty liver changes in diabetic patient.

Patient and method: This is Cross section study up on diabetic patient attending AL-Imamain AI-Kadhimiyain teaching hospital during the period from October 2018 – February 2019.

A total 50 individual had been included in the study sample. The patients were of both sexes between age of 20-89 years. To be included in the study should be diabetic patient and after exclusion criteria, send them for AST, ALT, lipid profile and ultrasound.

Results: Of the 50 diabetic patients enrolled in this study sample, 29 (58%) presented with fatty liver. The prevalence rate among females (60%) was higher than for males (55%).

The highest prevalence of NAFLD was recorded in the age group of 60-69 years at 34.5%. fatty liver during age 40-49 more male as its less in premenopausal but female number increase at postmenopausal reaching more than male at age 60-89.fatty liver was increased in patients with long duration of diabetic mellitus more than 10-15 years.

Conclusion:NAFLD is a common association of DM patient observed in the current study demonstrates an alarming public health problem. fatty liver more among DM type2. It was more in females than males, the duration of diabetic mellitus related to occurrence of fatty liver. Lab test and ultrasound lack sensitivities and specificity, so doing CTscain or MRI to see fatty changes in liver to confirm diagnosis.

Contents

List of tables

List of figures

List of abbreviation:

Content	Symbols
Non alcoholic fatty liver disease	NAFL
Diabetic mellitus	DM
Aspartate aminotransferase	AST
Alanine aminotransferase	ALT
Triglycerides	TG
Low density lipoprotein	LDL
Computerized tomography	CT
Magnetic resonance image	MRI

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بسم الله الرحمن الرحيم

وعلمك ما لم تكن تعلم

وكان فضل الله عليك عظيما

صدق الله العلي العظيم

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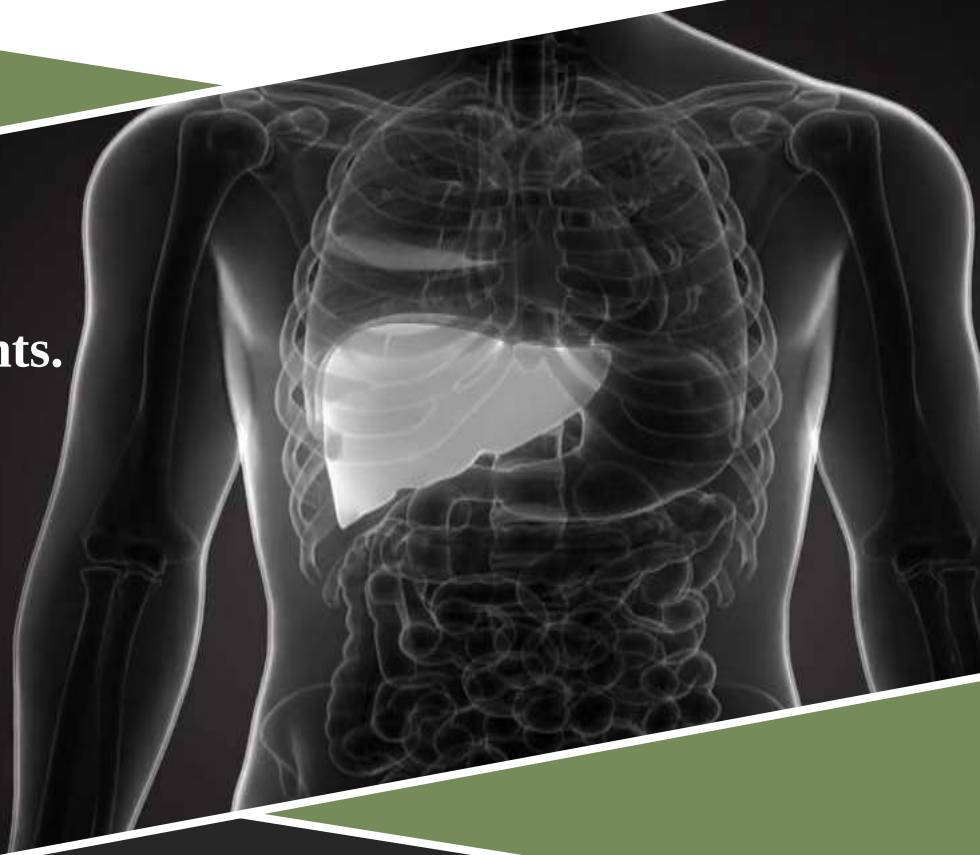
وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ

فرع الطب الباطني

Prevalence of fatty liver changes in diabetic patients.



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By:

Eelaf Abd Al-Kareem AI-Jawaheri

Supervised By:

Dr. Ali Sameer musa AL-Shammaa

F.I.C.M.S

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