A DISSERTATION ON "**NONALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETES MELLITUS - AN INDEPENDENT PREDICTOR FOR MACROANGIOPATHY AND MICROANGIOPATHY"**

A Dissertation Submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI

In Partial Fulfilment of the Regulations

For the Award of the Degree of

M.D. (GENERAL MEDICINE) - BRANCH – I

GOVERNMENT KILPAUK MEDICAL COLLEGE

CHENNAI

April - 2014

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled "**A DISSERTATION ON "NONALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETES MELLITUS - AN INDEPENDENT PREDICTOR FOR MACROANGIOPATHY AND MICROANGIOPATHY"** is a bonafide work done by **Dr. K.MOHANRAJ** Post Graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under our able guidance and supervision in partial fulfilment of the Rules and Regulations of **The Tamilnadu Dr.M.G.R.Medical University** for the award of **M.D. Degree Branch I, (General Medicine)** during the Academic period from May 2011to April 2014.

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DECLARATION

I solemnly declare that the dissertation entitled "**A STUDY ON "NONALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETES MELLITUS - AN INDEPENDENT PREDICTOR FOR MACROANGIOPATHY AND MICROANGIOPATHY"** was done by me at Kilpauk Medical College, Chennai under the able guidance and supervision of **Prof. Dr.K.T.JAYAKUMAR, M.D.,** Professor, Department of General Medicine, Government Royapettah Hospital, Chennai.

This dissertation is submitted to **The Tamilnadu Dr. M.G.R. Medical University, Chennai** towards the partial fulfilment of requirements for the award of the degree of **M.D. Branch -I General Medicine**.

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ACKNOWLEDGEMENT

I sincerely thank **Prof.Dr.P.Ramakrishnan, M.D., D.L.O.,** Dean, Kilpauk Medical College, Chennai for permitting me to utilize the facilities needed for this dissertation work.

I would like to express my special thanks to beloved **Prof.Dr.N.Gunasekaran, M.D., D.T.C.D.,** Director and Superintendent, Institute of Non Communicable Diseases, Government Royapettah Hospital, Professor and Head of the Department of General Medicine, Kilpauk Medical College and Hospital, Chennai for permitting me to carry out this study and for his constant encouragement and guidance.

I also express my sincere gratitude to **Prof.Dr.K.T.Jayakumar, M.D.,** my Unit Chief and Professor of Medicine for his guidance and constant support during the entire period of my study.

I am immensely thankful to **Prof.Dr.R.Sabaratnavel, M.D., Prof.Dr.S.Mayilvahanan, M.D.** for their help and guidance rendered during the entire period of my work.

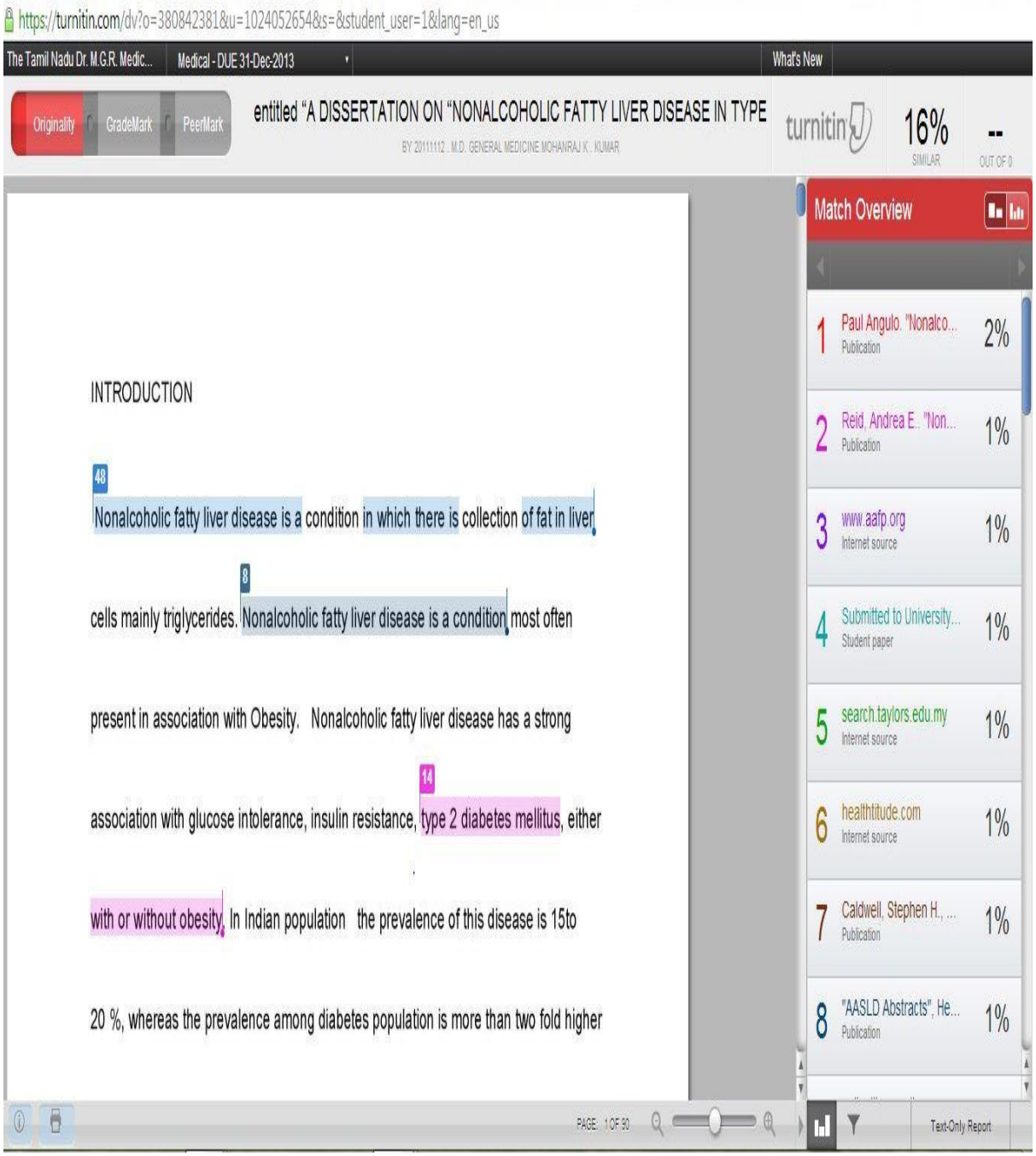
I wish to thank **Dr.K.Manickam M.D.,** Medical Registrar**, Dr Shaik Sulaiman Meeran M.D, Dr.T.Ramesh Kumar M.D, Dr.Swarnalatha, M.D., Dr.K.E.Govindarajullu M.D,** Assistant Professors, Department of

Medicine,Government Royapettah Hospital for their valuable suggestions and support throughout this work.

I also extend my thanks to the Statistician and all the laboratory technicians for their valuable support throughout my dissertation work.

I also thank my parents **Mr.R.Kumar**, and **Mrs.K.Saroja** siblings, colleagues, friends and staff of our hospital for their support of this work.

Last but not the least, with sincere gratitude; I thank all the patients who contributed so much to this study.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INTRODUCTION
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Nonalcoholic fatty liver disease is a condition in which there is collection of fat in liver
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cells mainly triglycerides. Nonalcoholic fatty liver disease is a condition most often
present in association with Obesity. Nonalcoholic fatty liver disease has a strong
14
association with glucose intolerance, insulin resistance, type 2 diabetes mellitus, either
with or without obesity. In Indian population the prevalence of this disease is 15to
20 %, whereas the prevalence among diabetes population is more than two fold higher
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CONTENTS

A DISSERTATION ON "**NONALCOHOLIC FATTY LIVER DISEASE IN TYPE 2 DIABETES MELLITUS - AN INDEPENDENT PREDICTOR FOR MACROANGIOPATHY AND MICROANGIOPATHY"**

INTRODUCTION

Nonalcoholic fatty liver disease is a condition in which there is collection of fat in liver cells mainly triglycerides. Nonalcoholic fatty liver disease is a condition most often present in association with Obesity. Nonalcoholic fatty liver disease has a strong association with glucose intolerance, insulin resistance, type 2 diabetes mellitus, either with or without obesity. In Indian population the prevalence of this disease is 15to 20 %, whereas the prevalence among diabetes population is more than two fold higher (50 to 75%). There is very strong association between nonalcoholic fatty liver disease and type 2 diabetes mellitus especially in obese individuals. . Hyperlipidemia is a risk factor for the development of nonalcoholic fatty liver disease. The incidence of non-alcoholic fatty liver disease is higher in the diabetic population which may act as a predictor for diagnosis of micro and macrovasuclar disease .The micro and macrovasuclar disease have a great impact on economy of the patient.

AIM OF THE STUDY:

1. To clarify the clinical characteristics of type 2 diabetic patients with non-alcoholic fatty liver disease (NAFLD)

2. To assess whether nonalcoholic fatty liver disease is related to diabetic micro and macroangiopathy.

METHODS AND MATERIALS:

This was an observational study done in Government Royapettah Hospital. The study recruited 100 patients who were admitted in the department of medicine and who attended diabetology department as out-patients. Those who fulfilled the inclusion and exclusion criteria were included in the study. In patients with type 2 Diabetes Mellitus, Fasting & postprandial glucose, lipid profile, liver function test with enzymes, Ultrasonogram, Urine spot albumin creatinine ratio, ECG, Carotid Doppler for Carotid Intimal Thickness, Ankle brachial index by Oscillometric method, urea, and creatinine will be done after obtaining written informed consent and the findings correlated to find out whether NAFLD is an independent indicator of angiopathy in these patients.

OBSERVATION AND RESULTS:

Out of 100 patients with diabetes 24 had retinopathy, 33 had peripheral arterial disease, 18had peripheral neuropathy, 12 patients had cerebrovascular accident, 30 had ischemic heart disease, 31 patients are in grade 2 diabetic nephropathy, 1 patient is in grade 3 diabetic nephropathy and 1 patient is in grade 4 diabetic nephropathy. Out of 40 patients with NAFLD 17 had retinopathy, 18 had peripheral neuropathy, 18 had ischemic heart disease, 10 had cerebrovascular accident. Among NAFLD patients with peripheral arterial disease 11 had mild disease 2 had moderate disease 1 had severe disease. Among NAFLD patients with diabetic nephropathy 29 patients are in grade 1 diabetic nephropathy, 11 patients are in grade 2diabetic nephropathy and there is no patient in grade 3 and grade 4nephropathy.the mean carotid intimal medial thickness is high among NAFLD group when compared with that of no NAFLD group (.789 Vs 0.698) . The prevalence of retinopathy (17 Vs 7), cerebrovascular accident (10 Vs 2), ischemic heart disease (18 Vs 12), peripheral neuropathy (18 Vs 0) is high among NAFLD group when compared to that of no NAFLD group all of which are statistically significant. The patients with NAFLD group had high BMI, high cholesterol, high blood pressure.

CONCLUSION:

The study concluded that the diabetic patients with nonalcoholic liver disease have high prevalence of ischemic heart disease, diabetic retinopathy, diabetic peripheral neuropathy, cerebrovascular accident and have increased carotid intimal medial thickness. The diabetic patients with nonalcoholic liver disease did not have any relation with diabetic nephropathy and peripheral arterial disease. The patients with NAFLD group had high BMI, high cholesterol, high blood pressure (both systolic and diastolic) high triglyceride levels.

Thus NAFLD in type 2 diabetes mellitus independently predicts of diabetic microangiopathy and diabetic macroangiopathy the characteristics of NAFLD in type 2 diabetes mellitus are studied.

Key words: nonalcoholic fatty liver disease, Type 2 diabetes mellitus, diabetic macroangiopathy, coronary heart disease.

INTRODUCTION

INTRODUCTION

Nonalcoholic fatty liver disease is a condition in which there is collection of fat in liver cells mainly triglycerides. Nonalcoholic fatty liver disease is a condition most often present in association with Obesity. Nonalcoholic fatty liver disease has a strong association with glucose intolerance, insulin resistance, type 2 diabetes mellitus, either with or without obesity. In Indian population the prevalence of this disease is 15to 20 %, whereas the prevalence among diabetes population is more than two fold higher (50 to 75%).

In upto 75 % of patients, nonalcoholic steatohepatitis may have insulin resistance which may be evident as acanthosis nigricans, diabetes mellitus, impaired glucose tolerance .The risk of nonalcoholic steatohepatitis is more than twofold higher in diabetic population when compared to that of non - diabetic individuals. The risk of cardiovascular disease is significantly increased when a patient with diabetes has nonalcoholic fatty liver disease. There is very strong association between nonalcoholic fatty liver disease and type 2 diabetes mellitus especially in obese individuals. Lean individuals also have a very good relationship between nonalcoholic fatty liver disease and insulin resistance. The diagnosis of nonalcoholic fatty liver disease requires a high degree of suspicion in diabetic population, because of the early progress to nonalcoholic steatohepatitis and cirrhosis. Hyperlipidemia is a risk factor for

the development of nonalcoholic fatty liver disease .A study showed an incidence of nonalcoholic fatty liver disease was 60% in patients with hyperlipidemia. Another study with living liver donors showed that hyperlipidemia was associated with more than 2 fold risk of steatosis.

The risk factors for nonalcoholic fatty liver disease are morbid obesity, type 2 diabetes mellitus, older age (>50 years) ,insulin resistance, and hyperlipidemia. Nonalcoholic fatty liver disease has been associated with many conditions which has mitochondrial injury as a key pathogenic mechanism. The hepatic component of Syndrome X is nonalcoholic fatty liver disease. The severity of nonalcoholic fatty liver disease increases with increasing number of components of Syndrome X namely, systemic hypertension, obesity, glucose intolerance and hyperlipidemia.

The incidence of non-alcoholic fatty liver disease is higher in the diabetic population which may act as a predictor for diagnosis of micro and macrovasuclar disease .The micro and macrovasuclar disease have a great impact on economy of the patient.

REVIEW OF LITERATURE

Review of literature

NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease was first described in the 1950s when fatty liver was present in a group of obese patients. Nonalcoholic steatohepatitis is part of nonalcoholic fatty liver disease which consist of fatty liver, nonalcoholic steatohepatitis, and nonalcoholic fatty liver disease - associated cirrhosis.

In 1980 at the Mayo Clinic, Ludwig and colleagues described 20 obese, diabetic, nonalcoholic patients who had same findings on liver biopsy to that of patients with alcoholic liver disease [1]. Following this observation the term nonalcoholic steatohepatitis was introduced for the first time. 3% of the general population were thought to have nonalcoholic steatohepatitis. Many patients who were previously identified as "cryptogenic" cirrhosis, in fact had liver disease due to nonalcoholic steatohepatitis. There will be a resolution of the steatosis once patients become catabolic because of cirrhosis.

DEFINITION

“The definition of nonalcoholic fatty liver disease (NAFLD) requires that

(a) There is evidence of hepatic steatosis, either by imaging or by histology and

(b) There are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders’’ .

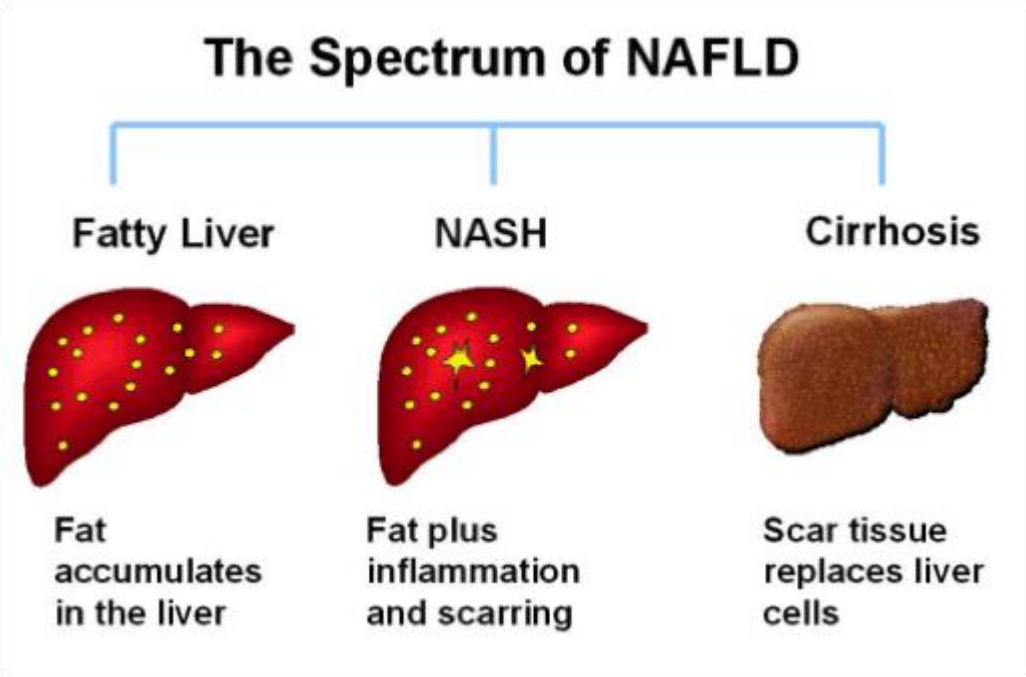


Figure 1show spectrum of nonalcoholic liver disease.

Nonalcoholic fatty liver disease

“Defined as fat exceeding 5–10% of weight in biopsy specimens”.

It also includes the term nonalcoholic steatohepatitis.

NONALCOHOLIC STEOTOHEPATITIS*:*

This nonalcoholic fatty liver disease will have "ballooned hepatocytes, inflammation, necroapoptosis (cell death), which is followed by fibrosis". This process usually begins around the central vein, which may lead to cirrhosis.

Non-nonalcoholic steatohepatitis fatty liver (NNFL*):*

Defined as "Nonalcoholic fatty infiltration with no or minimal inflammation, and no fibrosis". (Simple steatosis, Nonalcoholic fatty liver (NAFL), pure steatosis, bland steatosis.)

This form of fatty liver is more stable over time.

"Primary" NONALCOHOLIC FATTY LIVER DISEASE or NON ALCOHOLIC STEATOHEPATITIS*:*

"Typical nonalcoholic fatty liver disease or nonalcoholic steatohepatitis is associated with central obesity and often type 2 diabetes mellitus but without a specific, additional aetiology".

"The likelihood that many cases of "secondary" nonalcoholic fatty liver disease or nonalcoholic steatohepatitis represent unrecognized or exacerbated "primary"

nonalcoholic fatty liver disease or nonalcoholic steatohepatitis makes the term less useful".

*"**Secondary" NONALCOHOLIC FATTY LIVER DISEASE or NON ALCOHOLIC STEOTOHEPATITIS**:*

"Nonalcoholic fatty liver disease or nonalcoholic steatohepatitis associated with a specific, non-alcohol-related problem such as a drug- or toxin-induced cause"

***Toxin-associated steatohepatitis (TASH)**:*

"Nonalcoholic fatty liver disease or nonalcoholic steatohepatitis associated with a specific toxin or medication. Toxins implicated to date include petrochemical exposure in the oil industry and severe vinyl chloride exposure, methotrexate and tamoxifen".

*"**Presumed" NONALCOHOLIC STEATOHEPATITIS or NONALCOHOLIC FATTY LIVER DISEASE**:*

"Nonalcoholic fatty liver disease or nonalcoholic steatohepatitis based on abnormal liver enzymes, negative viral studies, and echogenic or 'bright' liver on ultrasonography consistent with fatty infiltration".

EPIDEMIOLOGY OF NONALCOHOLIC FATTY LIVER DISEASE

Figure 2

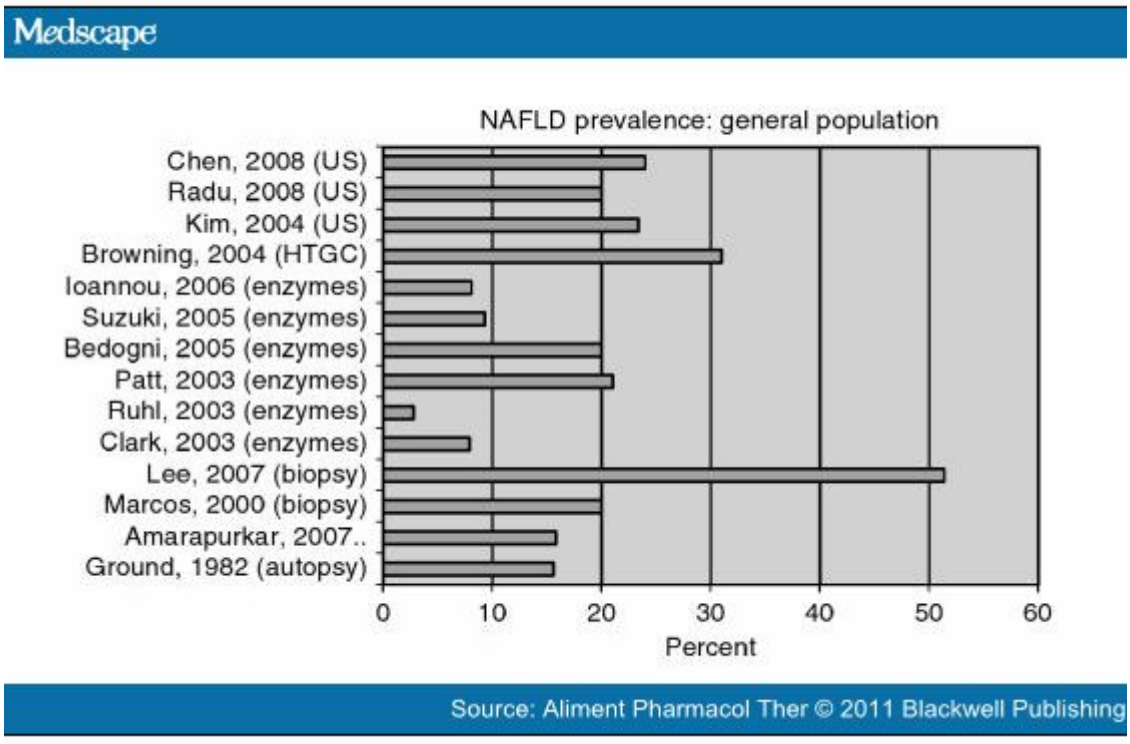


Fig.2 shows the prevalence of **nonalcoholic liver disease.**

The prevalence of nonalcoholic fatty liver disease was not known. Different studies were conducted throughout the world, each one of them are showing different prevalence rate. The prevalence of nonalcoholic fatty liver disease found by magnetic spectroscopy in Dallas study was 31% [2].

There was another study which was conducted in large population of 15,700 adults which showed the prevalence of nonalcoholic fatty liver disease was10%

to 24%. Obese individuals ranks first in the prevalence rate [3,4, 5]. Prevalence rate in obese patients who are not drinking was 76%. The name of this large study was the National Health and Nutrition Examination Survey [6]. Most of the patients with nonalcoholic fatty liver disease are in the age group of 40 to 60 years [7].

Figure 3

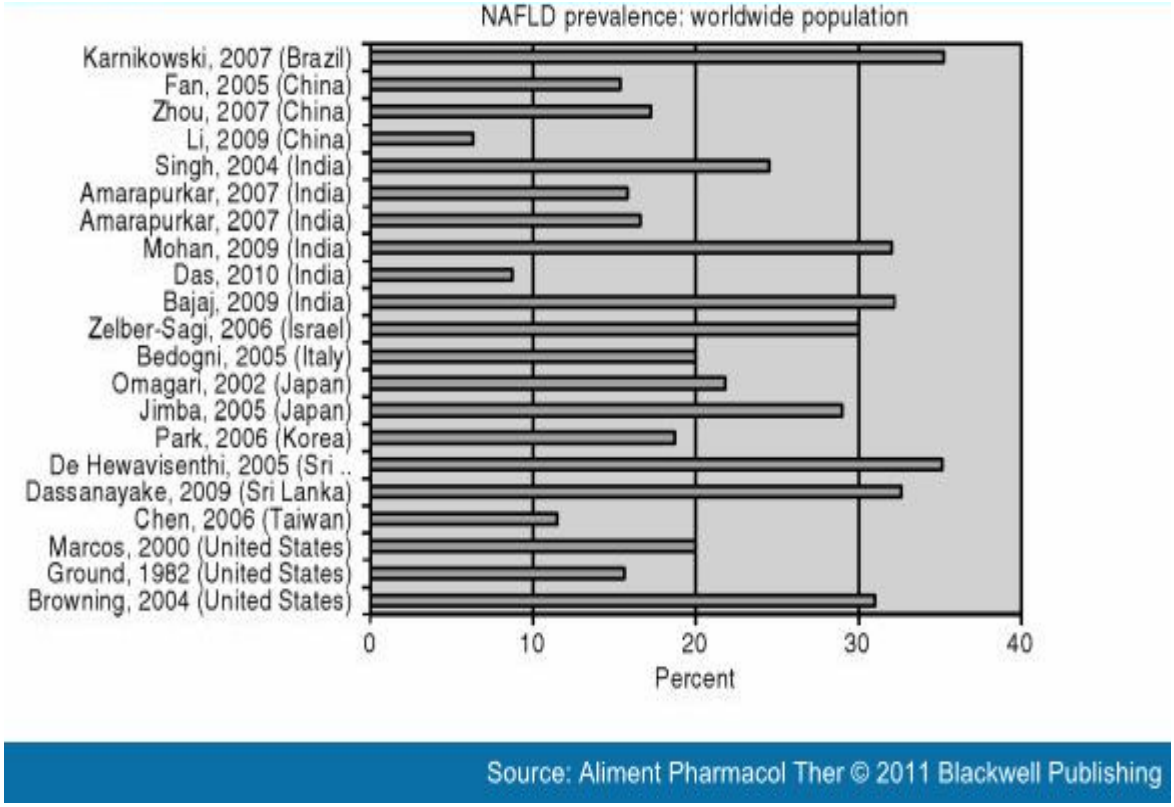


Fig.3 shows the worldwide prevalence of nonalcoholic liver disease**.**

In early studies it was found that the prevalence of nonalcoholic liver disease was high in females. In subsequent studies it was shown that the prevalence is the same in both male and female.

The prevalence of nonalcoholic fatty liver disease varies with the ethnicity. The highest prevalence was found in Hispanics which was about (45%) of non-alcoholic fatty liver disease [2]. The prevalence of nonalcoholic fatty liver disease among white individual was 33% and among African Americans was 24% [8] .The reason for difference in the disparity in different ethnic group was not known. The nonalcoholic fatty liver disease can occur as a familial cluster [9].

Figure 4

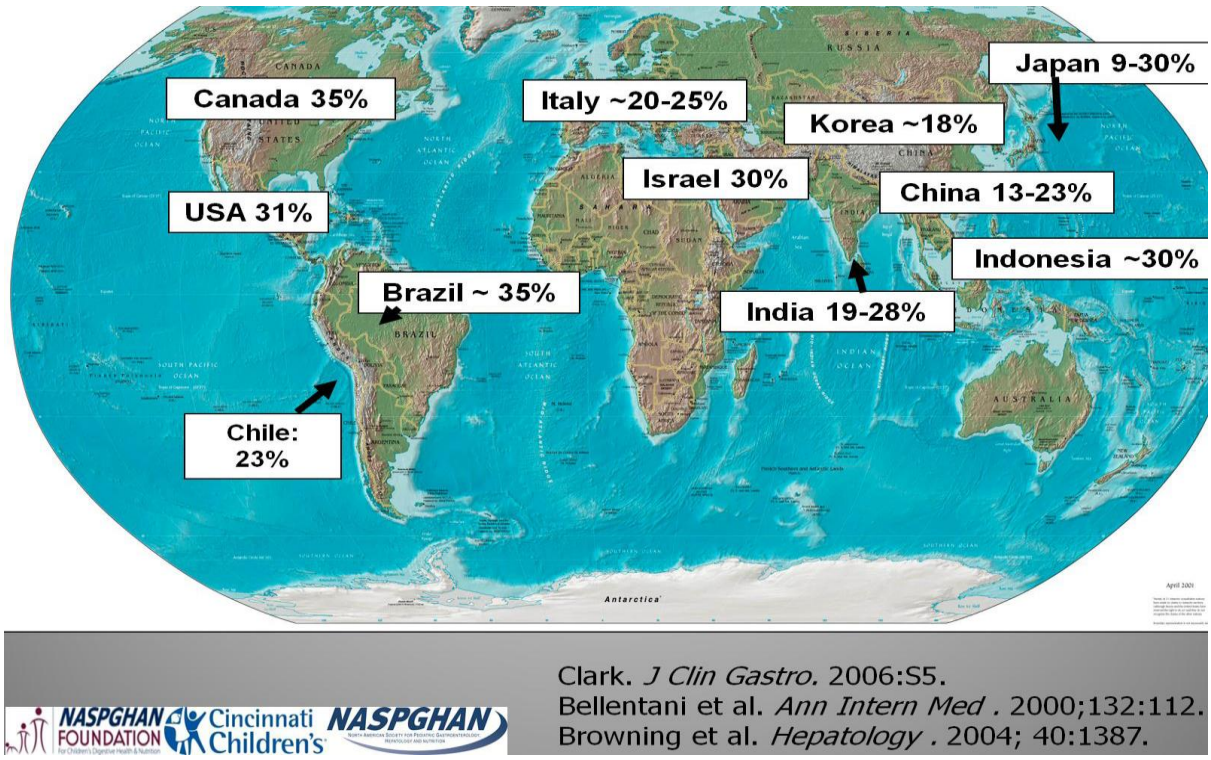


Fig.4 shows the prevalence of nonalcoholic liver disease across the world.

AETIOLOGY

Table 1

Acquired Metabolic Disorders
Diabetes mellitus
Dyslipidemia
Kwashiorkor and marasmus
Obesity
Starvation
Cytotoxic Drugs
l-Asparaginase
Azacitidine
Azaserine
Bleomycin
Methotrexate
Puromycin

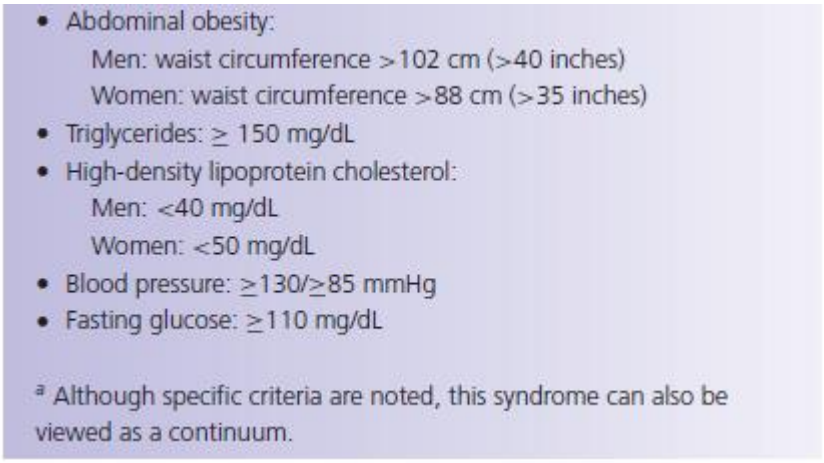
Drugs and Toxic compound
Amiodarone
4,4′-diethylaminoethoxyhexestrol
Dichlorethylene
Ethionine
Ethyl bromide
Estrogens
Glucocorticoids
Highly active antiretroviral therapy
Hydrazine
Hypoglycin
Orotate
Perhexilene maleate

Surgeries
Biliopancreatic diversion
Extensive small bowel resection
Gastric bypass
Jejunoileal bypass
Other Conditions
Industrial exposure to petrochemicals
Inflammatory bowel disease
Partial lipodystrophy
Jejunal diverticulosis with bacterial overgrowth
Severe anemia
Metabolic disorders
Abetalipoproteinemia
Familial hepatosteatosis
Galactosemia
Glycogen storage disease

Table 1 shows the aetiology of nonalcoholic liver disease.

“Adult Treatment Panel III clinical features of the metabolic syndrome”

Figure 5



- Abdominal obesity:
  - Men: waist circumference >102 cm (>40 inches)
  - Women: waist circumference >88 cm (>35 inches)
- Triglycerides: ≥ 150 mg/dL
- High-density lipoprotein cholesterol:
  - Men: <40 mg/dL
  - Women: <50 mg/dL
- Blood pressure: ≥130/≥85 mmHg
- Fasting glucose: ≥110 mg/dL

[a] Although specific criteria are noted, this syndrome can also be viewed as a continuum.

Fig.5 shows the features of metabolic syndrome.

PATHOGENESIS

THE “TWO-HIT HYPOTHESIS,”

The proposal for “two-hit hypothesis,” was first given by Day and James [9] in 1998.

“First hepatic insult”

Steatosis is the result of altered fatty acid metabolism. Steatosis is associated with several altered signalling pathways and cellular adaptations which render liver cells susceptible to a “second hit.”

"The second insult"

The genetic disruption and disruption in the environment plays as the second insult. Because of the second insult there will be hepatocyte inflammation followed by hepatocyte necrosis which results in the activation the fibrogenic cascade, which leads to fibrosis and then the cirrhosis.

Figure 6

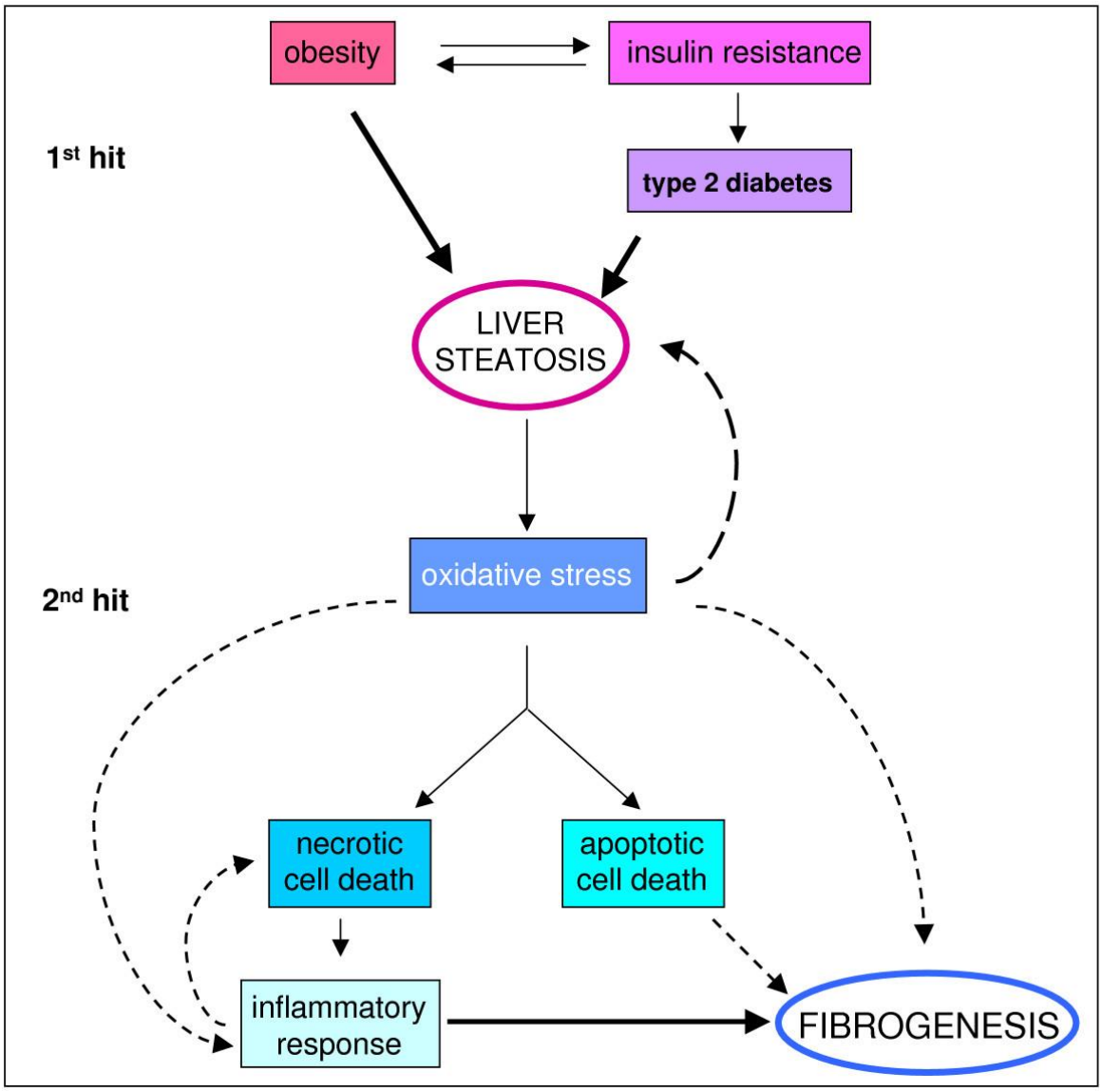


Fig.6 shows "***The two hit hypothesis"***.

The hallmark feature of nonalcoholic fatty liver disease is the steatosis of liver. The free fatty acid in the liver was first oxidized by mitochondria, which is then esterified into TGL. Phospholipids and cholesteryl esters are synthesised from the triglycerides and which is then secreted from the liver as VLDL cholesterol.

Fatty acid metabolism is under the strict control of hormones like insulin, growth hormone, glucagon and catecholamine. There is triglyceride accumulation in the liver cell when fatty acid metabolism shifts from disintegration to synthesis. Whenever there is excess of free fatty acid there will be a shift. The excess fatty acid can be obtained either from intestine or from the adipose tissue. The shift usually occurs when the amount of free fatty acid supplied to the liver is more than the need for oxidation and the formation of cholesteryl esters and phospholipid. Accumulation of triglycerides usually occurs in the liver when the rate of lipoprotein synthesis decreases or when the liver is not able remove the lipids.

HYPERINSULINEMIA AND INSULIN RESISTANCE

The pathogenic mechanism in individuals with nonalcoholic fatty liver disease are insulin resistance and hyperinsulinemia. The insulin resistance and hyperinsulinemia play a key role in the pathogenesis of fatty liver in even thin individuals . [10, 11, 12] .

HISTOLOGY OF OBESE PATIENTS

Figure 7

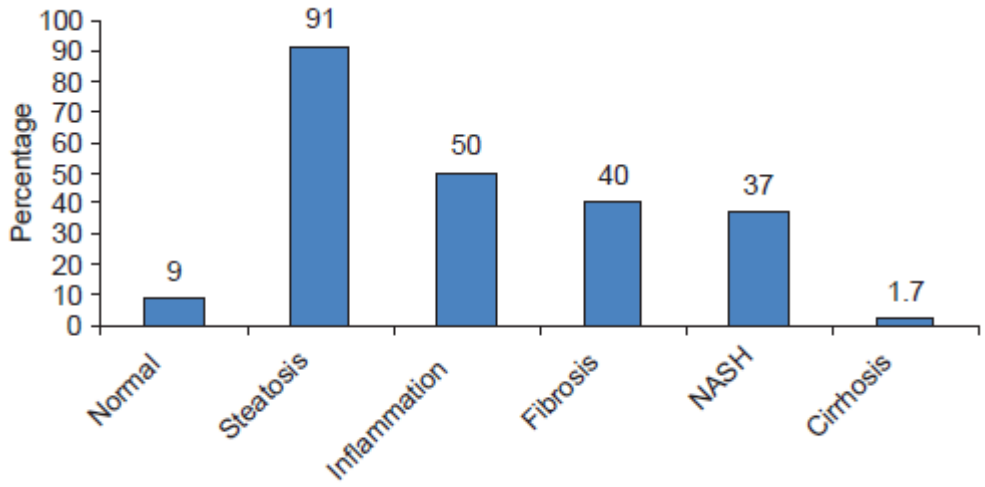


Fig.7 *shows the histology of obese patients. Normal histology was seen in 9% of individuals .1–2% of individuals had unidentified cirrhosis. Steatosis was present in 90% of the cases. Only one third cases with steatosis had met the criteria for nonalcoholic steatohepatitis. There was varying degrees of fibrosis in nonalcoholic steatohepatitis patients which was upto 40%.*

The insulin signalling pathway was disturbed by several important molecule like Tumour necrosis factor-α (TNF-α), free fatty acid, leptin, and, membrane glycoprotein PC-1which were present in obesity and hyperinsulinemia .The release of free fatty acid by insulin-resistant adipocytes

is abnormal .The insulin resistant adipocytes are present in diabetes and obesity. In diabetes there will be hepatic insulin resistance because of decreased signalling by insulin receptor substrate-1 because of increased free fatty acid [13, 14]. There will be decreased disposal of free fatty acid in Insulin resistance and hyperinsulinemic state which leads to fatty liver.

Figure 8

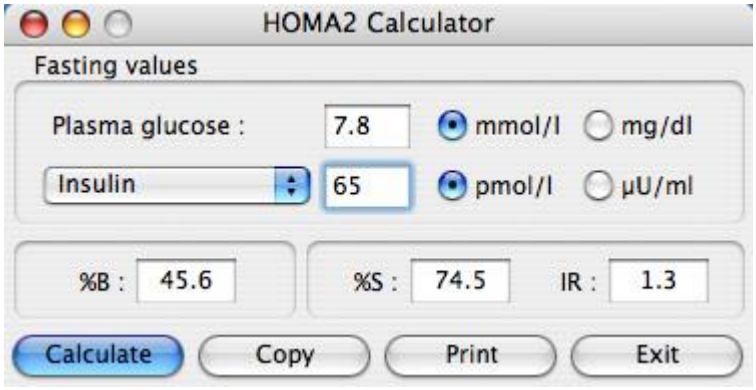


Fig.8 shows the HOMA2 calculator used for calculating insulin resistance.

The synthesis of fatty acid is stimulated by insulin in the liver. β-Oxidation of free fatty acid which occurs in mitochondria is down regulated by insulin . The release of triglycerides from the liver is blocked by insulin by increasing VLDL and apolipoprotein B-100 concentration in the liver cells [14, 15, 16].

Exocytosis of very low density lipoprotein containing vesicles is blocked by insulin. Hepatic triglyceride accumulation occurs in individuals with

nonalcoholic steatohepatitis because of reduced synthesis of hepatic apolipoprotein B-100[17].

Figure 9

Name	Formula	Level suggesting insulin resistance
HOMA	$\frac{\text{Fasting insulin (mU/L)} \times \text{fasting glucose (mmol/L)}}{22.5}$	> 1.8–2.0
QUICKI	1 / (log(fasting insulin μU/mL) + log(fasting glucose mg/dL))	< 0.35
Rough estimate	Fasting insulin × fasting glucose	> 700

Fig.9 shows formulas used in calculation of insulin resistance.

Figure 10

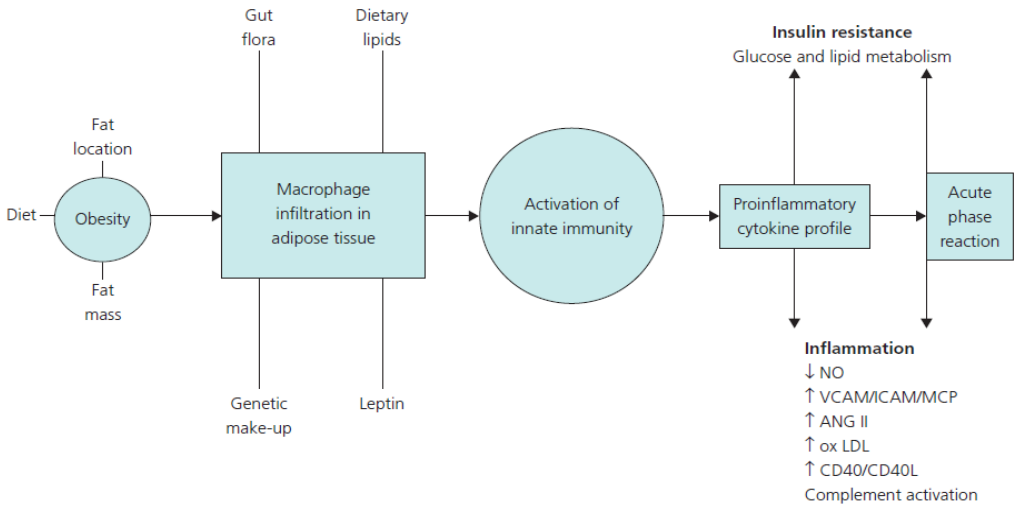


Fig.10 shows pathogenesis of nonalcoholic liver disease.

INSULIN RESISTANCE

Adipocytes secrete a number of mediators like adiponectin, leptin and TNF-α which are involved in the pathogenesis of insulin resistance in nonalcoholic fatty liver disease[18] .There will be interference in the insulin signalling by

TNF-α. This is done by *down regulation of IRS-1* signal which acts through serine phosphorylation. The insulin resistance which is present in the obese individual is mediated by *Jun N-terminal kinase (JNK).* The free fatty acid activates the *nuclear factor – κβ/ inhibitor kappa-β kinase (IKK-β)* which results in decreased liver insulin sensitivity [19, 20]. The activation of this pathway results in increased production of inflammatory cytokines such as TNF-α and interleukin (IL)-6[21, 22, 23].

Activation of the "inhibitor kappa-β kinase (IKK-β)/nuclear factor kappa β (NF-κβ)" pathway by free fatty acid may have a role in decreased liver insulin sensitivity.

ADIPONECTIN:

From the adipose tissue mainly from visceral**,** Adiponectin a cytokine which is a peptide is secreted. Adiponectin is in inverse proportion to the body weight and the body mass index [24]. The TNF-α is inhibited by adiponectin. Adiponectin supresses both plasma and hepatic TNF-α concentration. In insulin resistance, metabolic syndrome, diabetes mellitus, and obesity, the serum level of adiponectin is low.

Figure 11

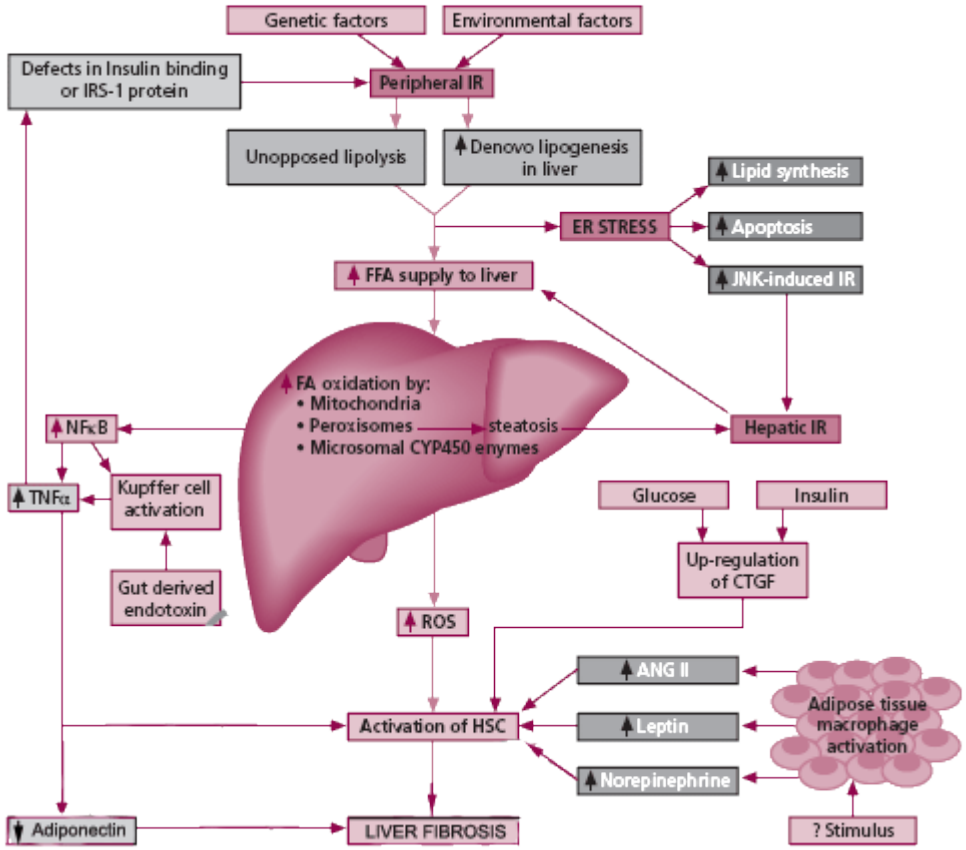


Fig.11 shows the role of cytokines in the pathogenesis of nonalcoholic liver disease.

Adiponectin will increase liver fatty acid metabolism, improves liver insulin resistance and also reduces liver triglyceride level which probably gives adiponectin a role as a therapeutic agent.

LEPTIN:

Adipocytes secrete a hormone called Leptin which is involved in controlling satiety (food intake). Maintaining the energy regulation is also under the control

of leptin. In insulin signalling, leptin has a role. The metabolism of glucose in peripheral tissue is under strict control of leptin. The partition of lipid between synthesis of triglyceride and mitochondrial β-oxidation is also under the control of leptin [27].

Leptin-deficient (ob/ob) mice had severe fatty liver and nonalcoholic steatohepatitis [25]. In humans obesity is the result of resistance to leptin. There is negative impact on signalling of insulin whenever there is increased leptin level. In obesity there will be long standing hyperinsulinemia which results in fatty liver. Serum leptin levels in individuals with nonalcoholic steatohepatitis correlate with the severe nature of fatty liver [26].

Adipocytokines and their effect on inflammation and insulin action:

The important factors involved in the development of fatty liver are increased insulin levels and insulin resistance. But we lack information about the subsequent insults which cause the progression from fatty liver to nonalcoholic steatohepatitis and nonalcoholic cirrhosis. There is a chronic oxidative stress because of activation of the microsomal enzyme, CYP2E1 and increased production of reactive oxygen species from the mitochondria [28].

The central pathogenic mechanism involved in the development of nonalcoholic fatty liver disease is lipid peroxidation. The increased amount of free fatty acid

in the blood is directly toxic to the liver cells and increased free fatty acid results in destabilization of lysosomes. The TNF-α is stimulated by increased free fatty acid [29].

Upregulation of cytochrome P450 isoenzymes occurs with increased free fatty acid levels, which results in increased production reactive oxygen species and there will be peroxidation of lipid. Peroxisomal proliferator-activated receptor-α (PPAR-α) is upregulated due to the raised intracellular levels of free fatty acid. PPAR-α upregulation results in oxidation of fatty acid and its removal.

Upregulation of PPAR-α result in increased oxidative free radicals formation from the derivatives of dicarboxylic acid. The affected individuals are prone to development of malignancy due to increased PPAR-α activation. The cell membranes are injured by the direct toxic effect of free fatty acid.

There is formation of a toxic compound namely fatty acid ethyl ether from free fatty acid. There is impairment in the function of mitochondria because of free fatty acid .The mechanisms which are protective against free fatty acid induced hepatotoxicity is lost when there is disruption of the function of mitochondria.

BACTERIAL ENDOTOXIN AND NONALCOHOLIC FATTY LIVER DISEASE

Bacterial endotoxin results in the development of nonalcoholic fatty liver disease. Nonalcoholic steatohepatitis is believed to develop from portal endotoxemia which occurs as a result of jejunoileal bypass surgery. The risk of nonalcoholic steatohepatitis after surgery can be reduced by antibiotics.

MITOCHONDRIAL CHANGES AND NONALCOHOLIC FATTY LIVER DISEASE.

The pathogenic processes involved in the formation of nonalcoholic fatty liver are altered liver energy metabolism and changes in the mitochondria. In nonalcoholic fatty liver disease there is increased free radical formation from the mitochondria and there is decrease in function of the respiratory chain in the mitochondria. Body mass index, TNF-α level, insulin resistance correlate with the changes in mitochondria [31, 32].

Uncoupling protein (UCP-2) present in the mitochondrial inner membrane is increased in Ob/ob mice. This protein causes leak in the proton, uncoupling ATP synthesis, and regulation of reactive oxygen species production. It also makes the fatty liver cells susceptible to the metabolic stress. The replacement of ATP in the ATP stores after its usage is reduced in nonalcoholic fatty liver

disease. The ATP stores are reduced due to structural changes in the mitochondria.

Mitochondria in patients with nonalcoholic fatty liver disease shows crystalline inclusions and their size is large [33] .Mitochondria assumes these changes as a result of oxidative process and it is an adaptive change. The mitochondrial changes which are present in nonalcoholic fatty liver disease are same as that in Wilson's disease and alcoholic liver disease.

When the nonalcoholic fatty liver disease is advanced, histological features suggestive of fibrosis are present. In liver sub endothelial space named as space of Disse contains stellate cells. When the stellate cells get activated it results in the proliferation and deposition of extracellular matrix mainly collagen type 3 and type 1.

The presence of growth factors, oxidative process, changes in extracellular matrix, inflammatory cytokines and angiotensin activates the liver stellate cells. In nonalcoholic fatty liver disease TGF- β production from the liver occurs as a result of peroxidation of lipids. The stellate cells in the liver are activated by TGF-β.The stimulus for the proliferation of stellate cells comes from the endothelium, leucocyte and kupffer cells by the release of TGF-β and PDGF [34].The release of connective tissue growth factor is stimulated by hyperglycemia and increased insulin levels, which is involved in the process of

fibrosis in non-alcoholic fatty liver disease [35]. The process of fibrosis in non-alcoholic fatty liver disease is perpetuated by leptin. Leptin stimulates sinusoidal endothelium and liver kupffer cells to produce TGF-β [36].

Nonalcoholic liver disease - a "multi-hit" process:

Pathogenesis of nonalcoholic fatty liver disease is a multi-hit process. Increased insulin levels and resistance to insulin results in fatty liver which is the first hit. The inflammatory process and the process of fibrosis which occurs after the formation of fatty liver involves series of mechanism.

1. Activation of liver kupffer cells

2. Peroxidation of lipids in the mitochondria

3. Oxidative damage to the mitochondria

4. Altered function in the mitochondria

5. Alteration in the cytokine levels

Figure 12

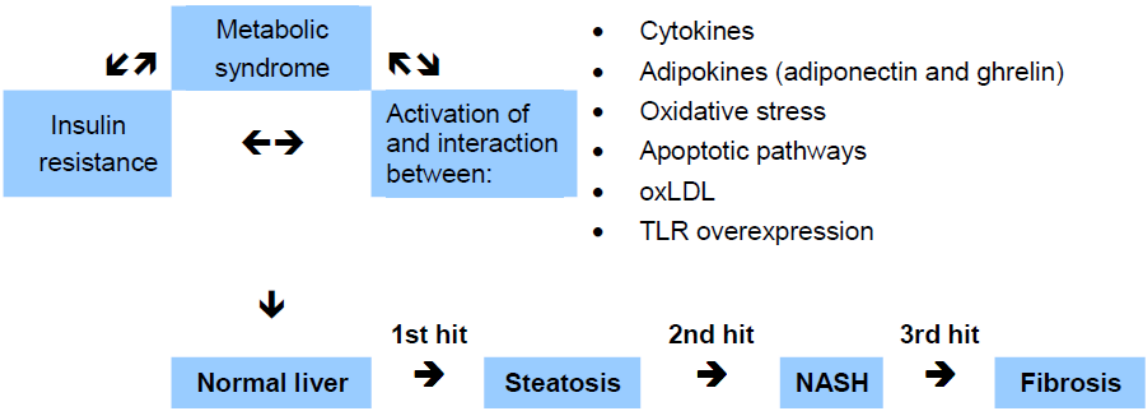


Fig.12 shows the "***multi hit hypothesis*** of nonalcoholic fatty liver disease".

THE "MULTI-HIT" HYPOTHESIS FOR NONALCOHOLIC STEATOHEPATITIS

The mice model which is deficit in S- adenosyl methionine will have severe form of fatty liver disease [37]. The increased glucose levels, increased insulin levels, resistance to insulin, increased body weight and fatty liver are produced by defects in the cholecystokinin –A receptor. This has been studied in a fatty rat model- "Otsuka-Long-Evans-Tokushima" [38]. The rats which are fed on high fat diet developed resistance to insulin, increased TNF-α levels, elevated oxidative process, lesions in the mitochondria and they will develop fibrosis at earlier age [39].

Figure 13

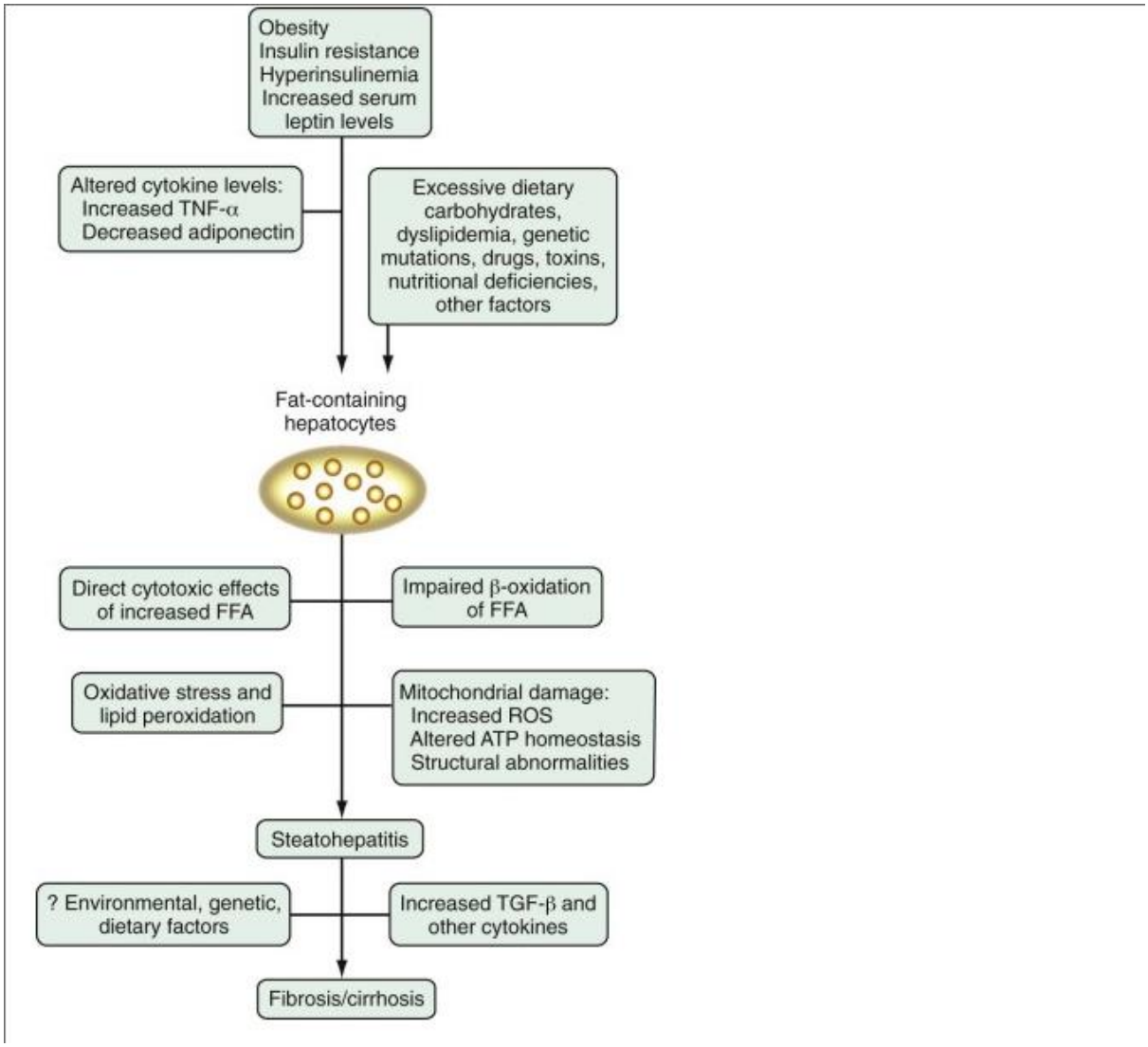


Fig.13 shows the pathogenesis of nonalcoholic fatty liver disease.

CLINICAL, LABORATORY, AND IMAGING FEATURES

The diagnosis of nonalcoholic fatty liver disease is mostly incidental. This is because of abnormal elevation of liver enzymes or hepatomegaly in screening.

The patients with nonalcoholic fatty liver disease are asymptomatic.

The symptoms of nonalcoholic fatty liver disease are

1. Vague pain in the upper right quadrant

2. Malaise

3. Fatigue

Upto 75% of patients with nonalcoholic fatty liver disease have hepatomegaly. It is very often difficult to make out hepatomegaly on physical examination, due to their increased body weight. Nonalcoholic fatty liver disease -associated cirrhosis will have the features of chronic liver disease like enlargement of spleen, spider naevi and abdominal distension.

Figure 14

SYMPTOMS	SIGNS	LABORATORY FEATURES
Common		
None (48%-100% of patients)	Hepatomegaly	Two- to fourfold elevation of serum ALT and AST levels AST/ALT ratio less than 1 in most patients Serum alkaline phosphatase level is slightly elevated in one third of patients Normal serum bilirubin and serum albumin levels and prothrombin time Elevated serum ferritin level
Uncommon		
Vague right upper quadrant pain Fatigue Malaise	Splenomegaly Spider angiomata Palmar erythema Ascites	Low-titer (less than 1 : 320) ANA Elevated transferrin saturation *HFE* gene mutation (C282Y)

Fig.14 shows the **Clinical and Laboratory Features of Nonalcoholic Fatty Liver Disease.**

In simple fatty liver patients the abnormal liver function tests are found in 50% of the individuals. In advanced nonalcoholic fatty liver disease patients the abnormal liver function tests are found in 80% of the individuals. The elevation of AST and ALT is usually up-to 1.5 to 4 fold, but they never exceed 10 times of the normal upper limit. The AST level is usually lower than the ALT level which is in contrast to the pattern seen in hepatitis due to alcohol.

The levels of GGTP and ALP are increased in nonalcoholic fatty liver disease. The Patients usually have normal level of bilirubin, prothrombin time and normal level of albumin. The levels of above marker are altered when the patient develops nonalcoholic fatty liver disease associated cirrhosis. Low titres of ANA may be found in one -fourth of the patients with nonalcoholic fatty liver disease [40]. The patients usually don't have HbsAg and AMA [41] .The patients must not have anti-HCV antibodies in order to confirm the diagnosis of nonalcoholic fatty liver disease. Patient must also have normal levels of α_1-antitrypsin and normal ceruloplasmin levels in serum.

Nonalcoholic fatty liver disease patients may have elevated levels of iron in serum and liver. In nonalcoholic fatty liver disease ferritin level in serum is increased in 20 to 50% of the patients. In advanced nonalcoholic fatty liver disease ferritin level in serum serves as a marker [42]. The incidence of familial hemochromatosis is not increasing in nonalcoholic fatty liver disease. The

severity in the histological finding doesn't have a relationship with clinical and lab measures.

Whenever we suspect nonalcoholic liver disease, in a patient with abnormally raised liver functions we usually order for an imaging. The most commonly ordered investigation in this setting is ultrasonogram. The finding in the ultrasonogram of the liver which suggests nonalcoholic fatty liver disease is increase in echogenicity and the liver appears very "bright". CT scan (spleen is higher in density than the fatty liver), and MRI of abdomen (T1 weighted imaging fat appears bright) are useful in the diagnosis of nonalcoholic liver disease.

The sensitivity for the diagnosis of nonalcoholic liver disease by USG and CT are 100% and 93% respectively when the liver fat is more than 33% with positive predictive value of 60% and 75% respectively [43].These imaging studies are helpful only in the diagnosis of nonalcoholic liver disease, but it doesn't predict the severity of nonalcoholic liver disease .

Figure 15

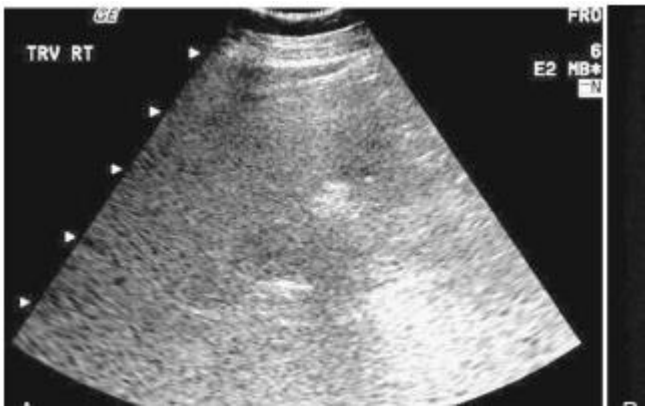


Fig.15 shows the USG finding in nonalcoholic liver disease -***increased echo texture.***

Figure 16

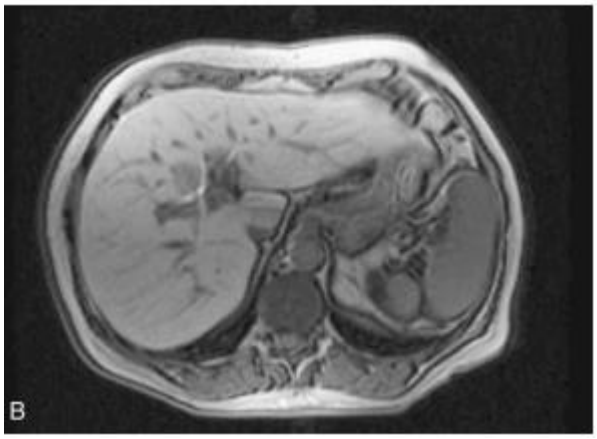


Fig.16 shows MRI findings in nonalcoholic fatty liver disease.T1-weighted MRI showing **"bright liver"**

HISTOPATHOLOGIC FEATURES:

The histological features of both alcoholic and nonalcoholic fatty liver disease are same. The spectrum includes

1. Fatty liver-steatosis

2. Steatohepatitis-fatty liver with inflammation of liver parenchyma with accompanying necrosis.

3. Cirrhosis

Figure 17

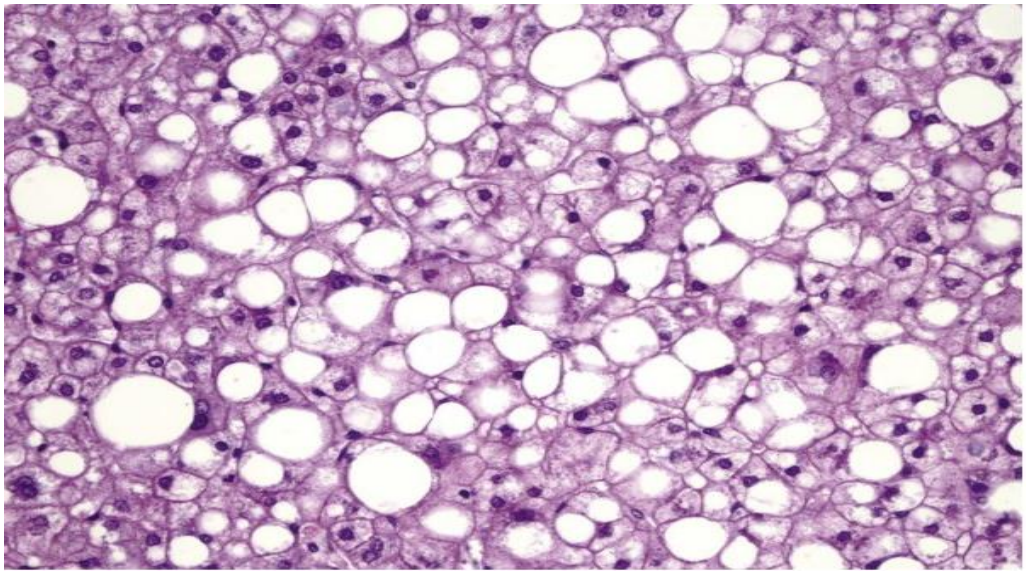


Fig.17 shows histological features of nonalcoholic liver disease.

HISTOLOGIC FEATURES OF FATTY LIVER.

1. Presence of macrovesicular steatosis (it is present in all the areas of hepatic lobule.)
2. Infiltration of WBC's mainly PMN's, lymphocytes are seen.
3. The nuclei are studded with glycogen.

Figure 18

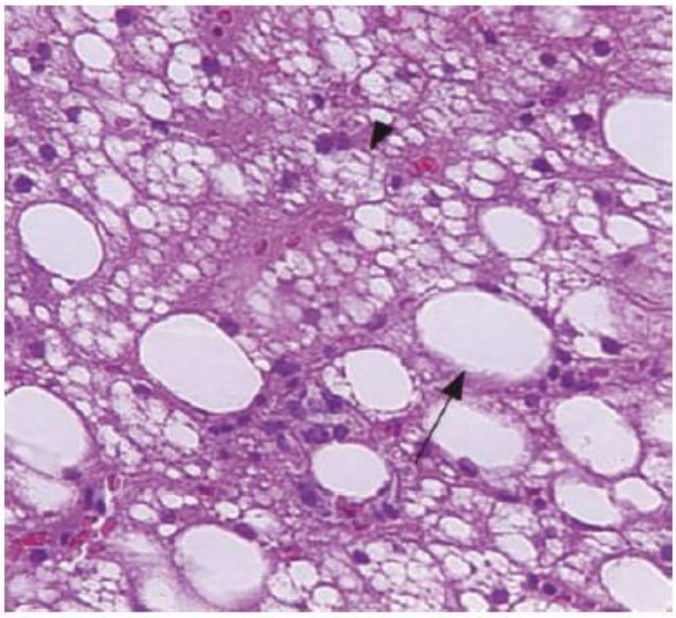


Fig.18 shows ***micro and macro vesicular steatosis***.

The advanced stage of nonalcoholic fatty liver disease is nonalcoholic steatohepatitis. It is very difficult to distinguish it from alcoholic liver disease by histology. Fatty liver is present in most of the patients. Central zone of the liver is affected primarily which then it involves entire liver. The individual's body mass index correlates with the degree of fatty liver.

The nonalcoholic liver disease patients will have severe degree of fat deposition than alcoholic liver disease [44]. Nonalcoholic steatohepatitis have lobular inflammation. Lobular inflammation is manifested by infiltration of PMNs, mononuclear cells and lymphocytes. According to the severity of nonalcoholic fatty liver disease, the degree of inflammation changes. In nonalcoholic fatty

liver disease the degree of inflammation is milder when compared to that of alcoholic liver disease [45]

Figure 19

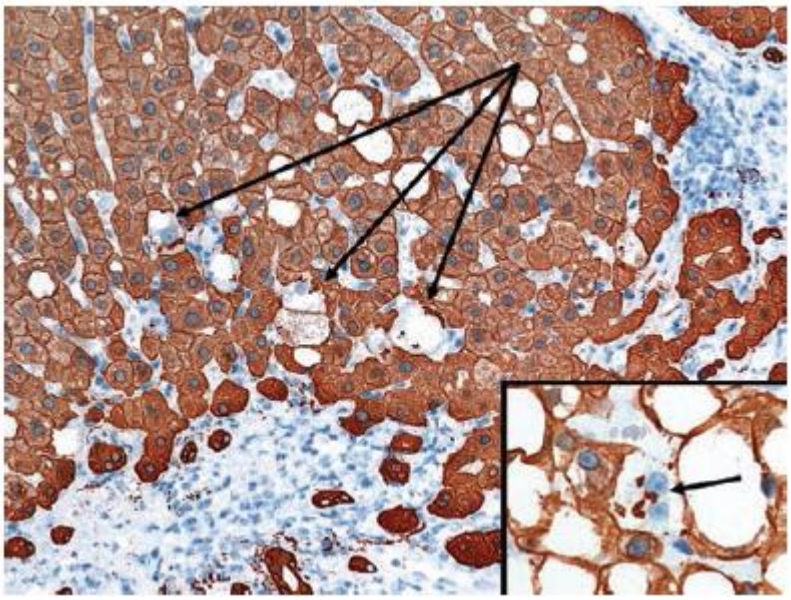


Fig.19 shows ***Antikeratin 8/18 immunohistochemistry***. The arrow shows ballooned liver cell are *"empty of keratin"*

The histological features of nonalcoholic fatty liver disease

1. The nuclei have glycogen inclusions.

2. The liver cells are ballooned.

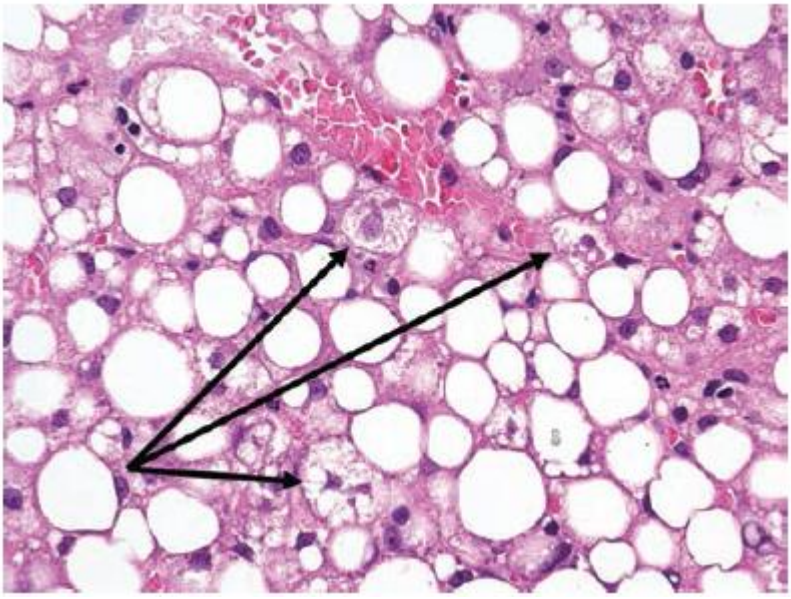
3. Necrosis of liver cell is present.

4. Mallory Denk bodies are seen.

5.50% of the individual have iron which is stainable.

6. In nonalcoholic steatohepatitis upto 37% to 84% of individuals may have fibrosis in periportal, perisinusoidal and pericellular.

Figure 20



In fig.20 the arrow shows liver cells with *"Mallory Denk bodies"*

When the patients have ballooning and necrosis of liver cells, the prognosis is bad [46]. The fibrosis in perisinusoidal region is very frequently seen in adults and it usually in zone 3.In nonalcoholic fatty liver disease, upto 7% to 16% of individuals have cirrhosis. In nonalcoholic fatty liver disease the morbid obese individual has the greatest risk of getting cirrhosis. When the patient develops nonalcoholic fatty liver disease associated cirrhosis, the classical feature in the histology of nonalcoholic fatty liver disease is lost which may lead us to make the wrong diagnosis of cryptogenic cirrhosis.

Figure 21

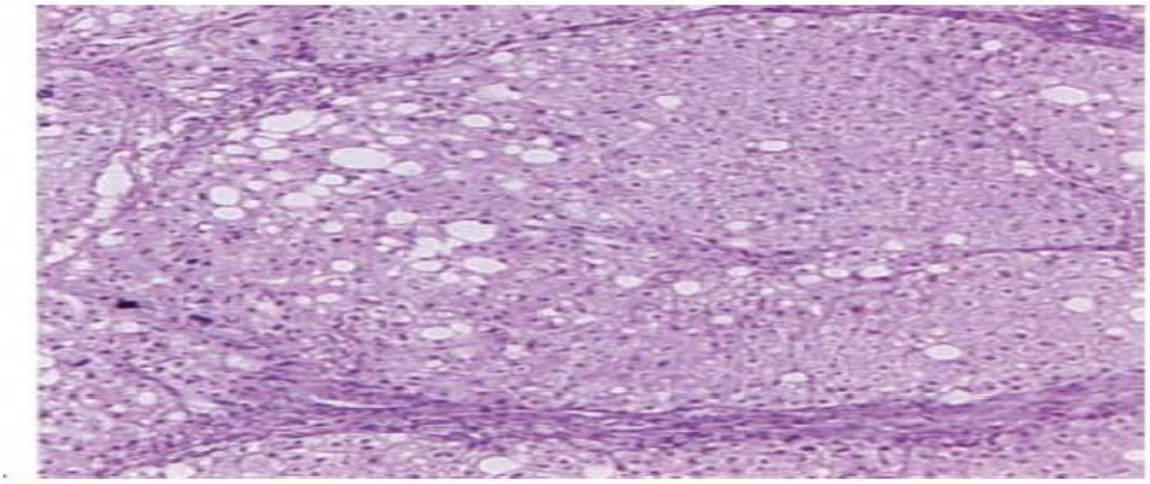


Fig.21 shows *nonalcoholic steatohepatitis with cirrhosis*.

Table 2

Grade	Brunt's scale[8]	Dixon's scale[9]
0	0% biopsed hepatocytes affected	No steatosis
1	< 33% biopsed hepatocytes affected	<5% of hepatocytes affected
2	33%-66% biopsed hepatocytes affected	5-25% of hepatocytes affected
3	>66% hepatocytes affected	25-75% of hepatocytes affected
4	—	>75% of hepatocytes affected

Table 2shows the different scales used in the histology of nonalcoholic fatty liver disease.

DIAGNOSIS

Diagnosis of nonalcoholic fatty liver disease can be established by

1. Imaging

2. Histology

We usually evaluate nonalcoholic fatty liver disease patients because of their long term elevation of liver function test with or without liver enlargement. We usually need history of the patient, examination, biochemical tests and imaging modality to exclude the secondary causes of steatosis.

Even if the patient doesn't have typical findings on imaging, it doesn't exclude the diagnosis of nonalcoholic fatty liver disease. We should rule out alcoholic liver disease first before making the diagnosis of nonalcoholic fatty liver disease. It is very difficult to differentiate nonalcoholic fatty liver disease and alcoholic liver disease by both clinical and histological methods. So we should make the diagnosis of nonalcoholic fatty liver disease only when the patient didn't take "significant amount of alcohol - consumption of less than 20 to 40 g of alcohol per day".

Table 3

S.NO	BATTERY OF INVESTIGATIONS
1.	Liver biochemical tests
2.	Complete blood count
3.	Prothrombin time
4.	Hepatitis B surface antigen,
5.	Anti-HCV
6.	Iron indices
7.	Ceruloplasmin in persons younger than 40 years of age,
8.	Antimitochondrial antibody
9.	α_1-antitrypsin

Table 3 shows investigation employed in nonalcoholic liver disease.

The Role of Liver Biopsy

The role of liver biopsy in nonalcoholic fatty liver disease has not been well established. The diagnosis of nonalcoholic fatty liver disease is usually made by excluding the causes of chronic liver disease by clinical and biochemical examination. So it is a diagnosis of exclusion.

Diagnosis of nonalcoholic fatty liver disease is made when ultrasonogram or CT shows fatty liver. Most of the individuals with nonalcoholic fatty liver disease

usually don’t undergo liver biopsy, because liver biopsy results are not going to change the management of nonalcoholic fatty liver disease. There is no clear cut relationship between clinical examination, biochemical tests and histology.

Some patients with normal liver function test will have advanced disease in biopsy. The quantity of “steatosis, necrosis and fibrosis” can be only assessed through liver biopsy. The best prognostic marker for nonalcoholic fatty liver disease is histology. It is advisable to do liver biopsy in patients who are suspected to have advanced form of nonalcoholic fatty liver disease because liver biopsy can influence the treatment.

INDICATION OF LIVER BIOPSY IN NONALCOHOLIC FATTY LIVER DISEASE [47]:

1. Overweight and obese individuals
2. Abnormal persistent elevation of liver function tests even after good glucose control and loss of weight
3. Advanced age
4. Metabolic syndrome with multiple components
5. AST/ALT > 1
6. Signs and symptoms of portal hypertension
7. Radiological evidence of fibrosis.

The liver biopsy is considered in above patients because the liver biopsy results may help us to treat the patient aggressively. It also ensures us to screen the patient for the future development of hepatocellular carcinoma and also helps the patient to participate in clinical trials.

DISADVANTAGES OF LIVER BIOPSY:

1. Costly

2. Invasive

3. Small risk of complications like pneumothorax, injury to the kidney, bile duct and bleeding manifestations.

Non-invasive Markers of Fibrosis in nonalcoholic fatty liver disease:

1. Serum α_2-macroglobulin

2. Apolipoprotein A-1

3. Haptoglobin

4. Total bilirubin, and GGTP levels,

5. Necroinflammatory activity index

6. Transient elastography (Fibroscan) [48]

7. Serum dehydro epiandrosterone levels [49]

8. Serum hyaluronic acid levels [50]

9. The Fibro Test [51]

Table 4

INTERPRETATION OF RESULTS:

Fibro test cut off value	Interpretation
0.7	Positive predictive value of 73% and Specificity of 98% for advanced fibrosis
0.3	Negative predictive value of 90% for advanced fibrosis.
0.3 – 0.7	Inaccurate Advised to do liver biopsy

Table 4 shows the interpretation of results of **fibro test**.

NON-ALCOHOLIC FATTY LIVER DISEASE FIBROSIS SCORE:

This score is formulated and validated by **Angulo** [52]. This score uses only Clinical and biochemical values.

Table 5

S.NO	Parameters	Interpretation
1.	Age	Positive predictive value-
2.	Body mass index	82 to 90%
3.	Blood sugar	Negative predictive value-
4.	Albumin level	88 to 93%
5.	AST/ALT ratio	Indeterminate-25 to 28%
6.	Platelet count	Do liver biopsy in them

Table 5 shows the parameters used in *nonalcoholic fatty liver disease fibrosis score*.

NATURAL HISTORY

Nonalcoholic fatty liver disease is a benign disease .When the patient doesn't have liver necrosis or fibrosis the prognosis is usually favourable [53]. They have only little chance of getting severe form of disease. Liver failure, cirrhosis hepatocellular carcinoma can develop in few patients of nonalcoholic fatty liver disease.

From 2003 to 2008, 215 patients have been studied in 5 retrospective studies using paired biopsy of liver [54, 55, 56]. They were followed for a period of

1 to 14 years. The progression in the histology of liver (fibrosis) was present in the 30 to 40% of individuals with non-alcoholic fatty liver disease. The histological course was stable in about 35 to 50% of individuals with non-alcoholic fatty liver disease. Histology improved in about 15 to 30% of persons with non-alcoholic fatty liver disease. There was a variable rate of development of fibrosis. There was no correlation between clinical picture and the histology.

There is no reliable marker for the prediction of course of nonalcoholic fatty liver disease. A large study with 420 individuals was conducted in Minnesota using definite cases of non-alcoholic fatty liver disease [57]. The diagnosis of nonalcoholic fatty liver disease was made in these patients using ultrasound. Among them, 3% developed cirrhosis over a period of 8 years. The common causes of death in these patients are malignancy, coronary artery disease and liver disease in that order. So, nonalcoholic fatty liver disease follows an indolent course. There was another study using 130 individuals with non-alcoholic fatty liver disease over a period of 20 years which confirmed the previous conclusions.

The mortality and morbidity were higher in nonalcoholic steatohepatitis individuals when compared with the general population. When compared with general population, the children with nonalcoholic fatty liver disease have decreased survival rate. The natural history of nonalcoholic fatty

liver disease can be assessed by the severity of the damage in the liver histology.

In nonalcoholic fatty liver disease when the patient has only steatosis without any signs of inflammation, they usually have a benign course .Upto 16 to 26% of patients with nonalcoholic steatohepatitis can progress to liver cirrhosis over a period of 20 years. At the time of diagnosis, upto one third of biopsy in nonalcoholic steatohepatitis individuals show fibrosis of liver in the advanced stage and 16% show established liver cirrhosis.

Most of the cases which are previously identified as cryptogenic cirrhosis are actually nonalcoholic fatty liver disease associated cirrhosis [58, 59, and 60]. In these patients the histological features of nonalcoholic steatohepatitis or nonalcoholic fatty liver disease is replaced by plain cirrhosis. Hepatocellular carcinoma can develop from nonalcoholic fatty liver disease associated cirrhosis. The prevalence of hepatocellular carcinoma in nonalcoholic fatty liver disease associated cirrhosis ranges from 0.6 to 3% .In Japanese study it has been shown that the cumulative risk of getting hepatocellular carcinoma in non-alcoholic fatty liver disease patient is as high as 15%.

Whenever patient develops nonalcoholic fatty liver disease associated cirrhosis we should consider liver transplantation in them .However there is a recurrence of nonalcoholic fatty liver disease associated cirrhosis in the liver transplanted

individuals. The cause of recurrence of nonalcoholic fatty liver disease associated cirrhosis in them is not known.

Figure 21

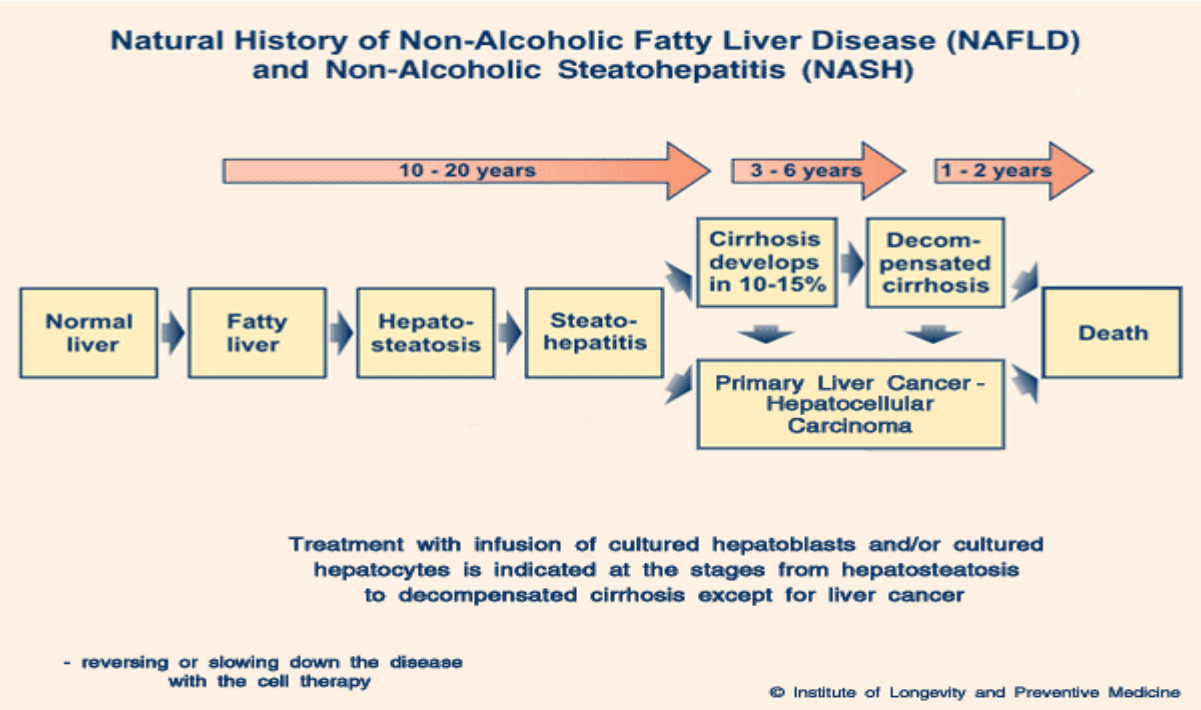


Fig.21 shows the natural history of nonalcoholic fatty liver disease.

Several numbers of genes have been thought to play a role in the natural history of nonalcoholic fatty liver disease and are yet to be revealed. The survival rate of patients with nonalcoholic fatty liver disease was higher than that of the patient with alcoholic liver disease though they share common histological picture. A study compared the outcome of nonalcoholic fatty liver disease associated cirrhosis and hepatitis C virus associated cirrhosis [61]. The study

revealed the outcome was similar in both groups; however incidence of development of hepatocellular carcinoma is low in the first group.

Table 6

S. No	RISK FACTORS FOR ADVANCED DISEASE
1	Older age
2	Obesity
3	Diabetes mellitus
4	AST/ALT>1
5	BMI>28 kg/m^2
6	Triglyceride level > 1.7 mmol/L
7	Necroinflammatory activity in liver
8	Systemic hypertension
9	High insulin resistance index
10	?women gender

Table 6 shows the risk factors for advanced nonalcoholic fatty liver disease**.**

Figure 22

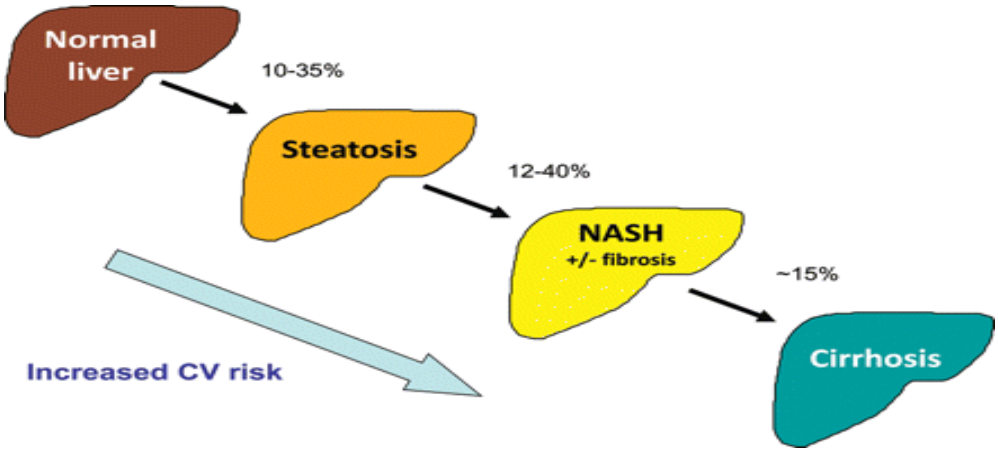


Fig.22 shows spectrum of NAFLD and its progression.

TREATMENT

The therapy which is optimum for the treatment of nonalcoholic liver disease is not known. Till now, no randomized control trials have shown any improvement in inflammation, steatosis and fibrosis.

In olden days the treatment for non-alcoholic fatty liver disease emphasised

1. Reduction in the body weight

2. Withdrawal of toxin and drugs from the patients.

3. Control of blood sugar in case of diabetes.

4. Control of cholesterol levels

Figure 23

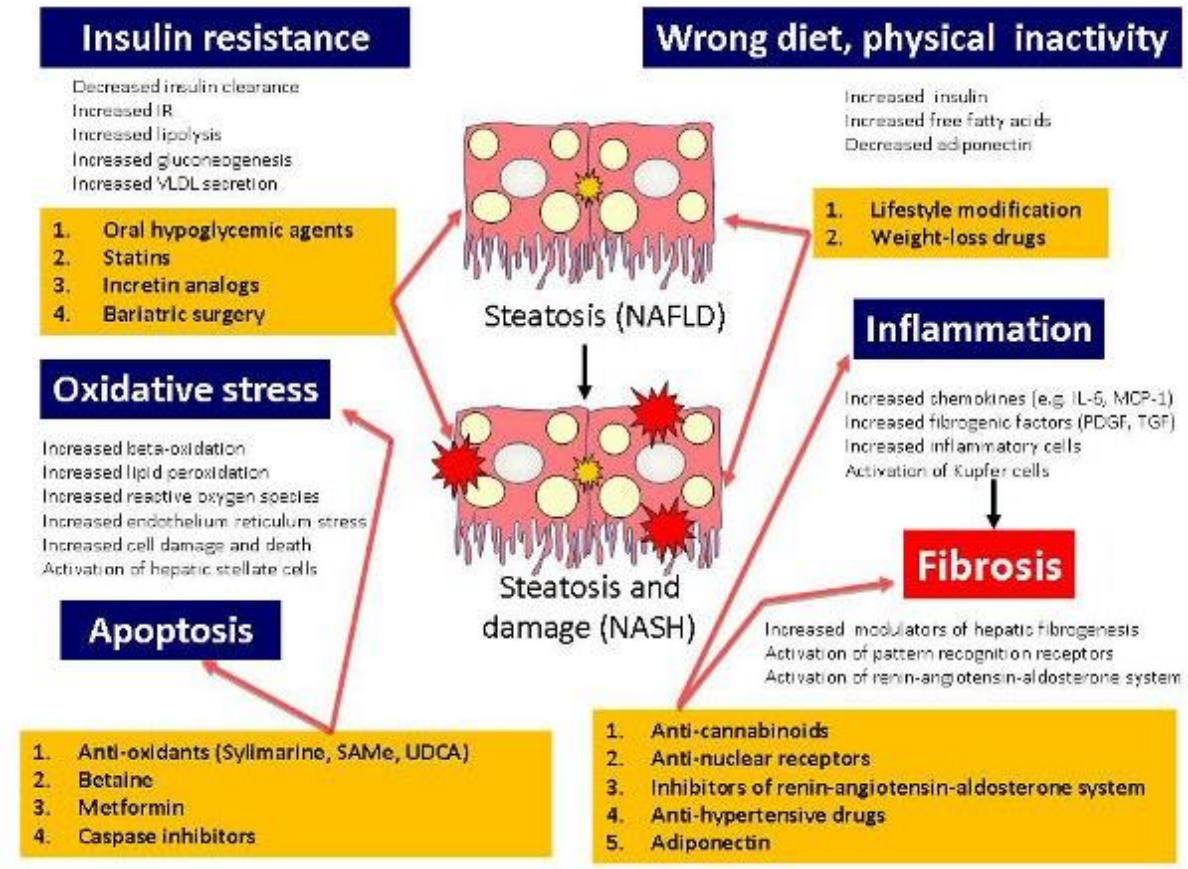


Fig.23 shows pathogenesis and the management of NAFLD.

In patients with nonalcoholic fatty liver disease exercise and diet appears to be beneficial. Exercise and diet show improvement in imaging and laboratory values [62, 63, 64].When the loss of weight is sustained by nutritional intensive counselling, there is improvement in the histology [65] .In few studies it was shown that weight reduction with orlistat results in improvement of liver histology and liver function test [66 67]. Orlistat is a reversible inhibitor of lipases from the stomach and the pancreas.

Figure 24

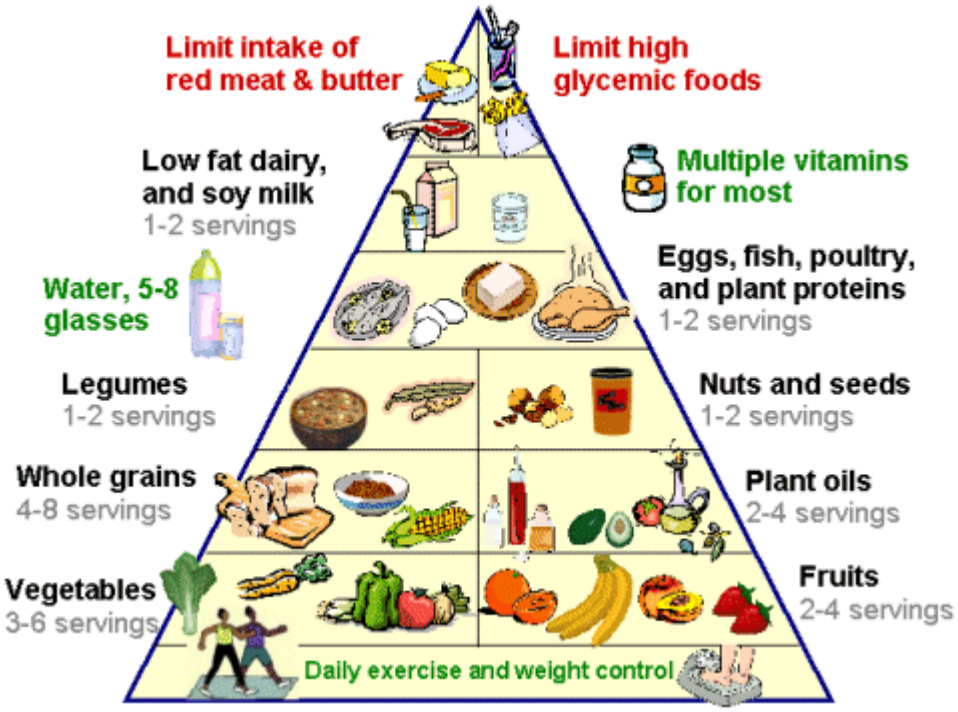


Fig.24 shows the dietary plan in patients with nonalcoholic liver disease.

In few studies it was shown that weight reduction with Bariatric surgery results in improvement of liver histology and liver function test [68-72]. It also results in

1. Maximal loss of weight.

2. Improvement in the sensitivity of insulin.

3. Normalization of metabolic parameters which are involved in the pathogenic process of nonalcoholic fatty liver disease.

4. The expression of inflammatory mediators from the liver are reduced.

5. Improvement in the histology of liver.

Figure 25

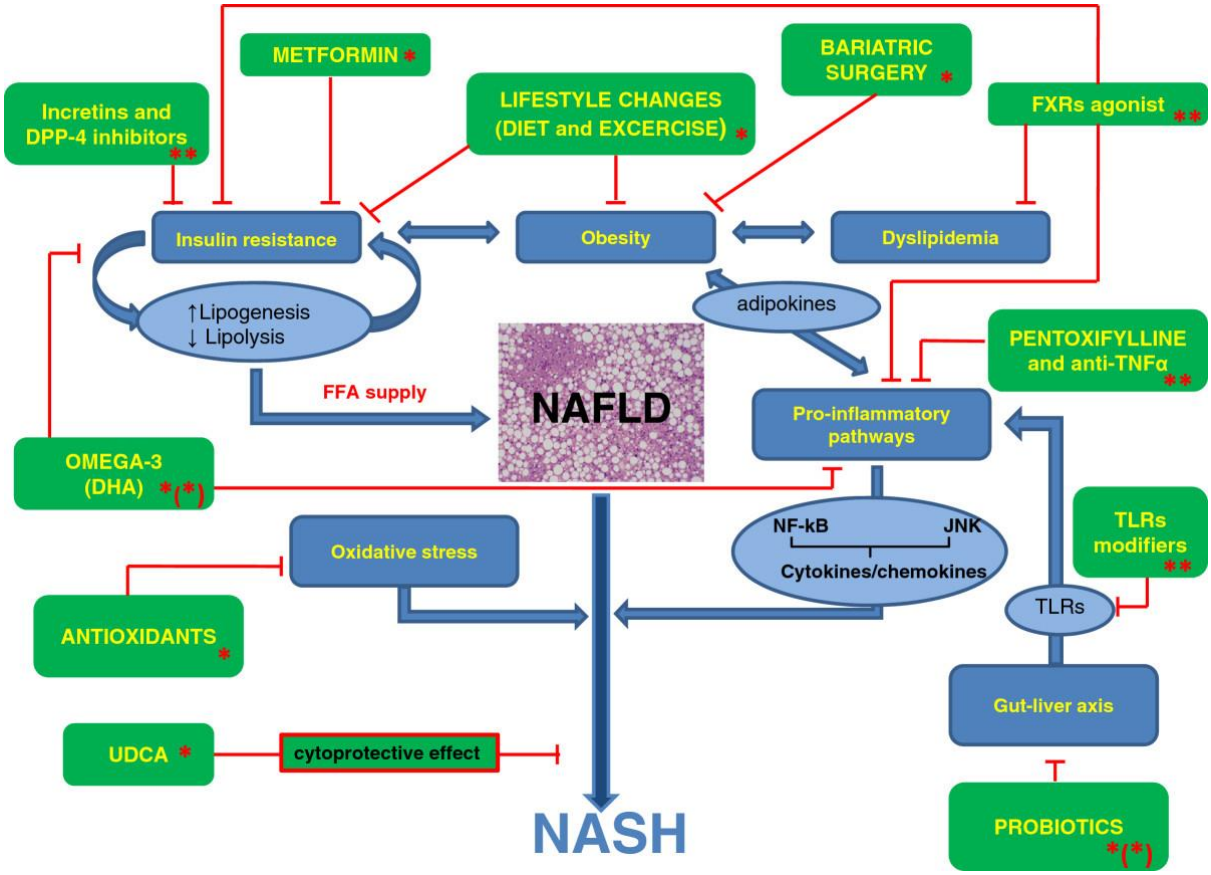


Fig.25 shows the modalities employed in the treatment of nonalcoholic fatty liver disease.

The effect of loss of weight achieved by drugs, surgery or exercise was not well established in the studies [73]. Though there are no clear cut guidelines to say whether weight loss is beneficial or not, it is better to advice weight loss in obese patients. It is very difficult to maintain sustainable weight loss. In obese individuals rapid weight loss results in nonalcoholic fatty liver disease [74]. The

very important thing in loss of weight is the rate at which weight reduction occurs.

Antioxidants

Vitamin E

Vitamin E, is a powerful antioxidant, which has been used for treatment of nonalcoholic fatty liver disease .Vitamin E is a very well tolerated drug., in most of studies it was shown that treatment with vitamin E results in the improvement of liver function test, liver imaging and its histology[75,76] .Vitamin E has negative effects on cardiovascular system , there should be caution in using this drug in the treatment of non-alcoholic fatty liver [77].

Betaine:

A choline metabolite betaine increases S –adenosylmethione levels and it also reduces the oxidative damage in the cell [78].

Superoxide dismutase, *N*-acetylcysteine and ragaglitazar may be used in non-alcoholic liver disease, but the human studies are lacking [79, 80].

Insulin-Sensitizing Agents:

The association between non-alcoholic fatty liver disease and increased insulin level, resistance to insulin gives a target for therapy with insulin sensitizers.

METFORMIN:

It is an oral hypoglycemic agent that belongs to the class of a biguanides.

1. It reduces the state of hyperinsulinemia
2. Improves sensitivity of insulin in liver
3. Resolves hepatomegaly and
4. Resolves liver steatosis in ob/ob mice[81]

In trials the effect of this drug was not too good [82, 83].

THIAZOLIDINEDIONES:

It acts through PPAR-α receptors and it has agonistic action over this receptor. The liver, muscle and adipose tissue have PPAR-α receptor. PPAR-α cause differentiation of cell and reduces the rate of lipolysis and free fatty acid release from the adipocytes. Thiazolidinediones increase the sensitivity of insulin and improves disposal of glucose in muscle and reduces glucose output from the liver. Pioglitazone and Rosiglitazone, have lower rates of liver toxicity. Both have been studied in different 48-week trials in individuals with nonalcoholic steatohepatitis [84, 85]. In both the trails it has been shown that treatment with thiazolidinedione's was tolerated well. It was associated with improvement in sensitivity of insulin, improvement of liver function test, and

improvement in liver histology. The side effects of both TZD's are gain in weight (4.0% to 7.3%) and increase in adiposity.

Iron Reduction:

In nonalcoholic fatty liver disease patients, the levels of ferritin and the iron are high in the serum. The elevated level of iron in the liver is believed to be involved in the pathogenesis of nonalcoholic fatty liver disease. The elevated level of iron in the serum induces inflammation in the liver. Therefore, removal of iron from the body is believed to help the patients with nonalcoholic fatty liver disease by decreasing the levels of sugar, insulin in the plasma and normalizing the liver function test [86, 87].

"The relationship between iron and insulin is complex" but depletion of iron may have the insulin-sparing effect [88] .It results in enhanced transport of glucose in the skeletal muscle. It also reduces the metabolism and the removal of insulin from the liver.

Lipid-Lowering and cytoprotective Agents:

In some trials the usefulness of UDCA, a cytoprotective drug and gemfibrozil, a lipid-lowering agent has been studied with different results.

Gemfibrozil may be used in the treatment of nonalcoholic fatty liver disease and its treatment showed improvement in biochemical parameters in 74% of individuals in the treatment group [89]. In nonalcoholic steatohepatitis

treatment with atorvastatin showed improvement in biochemical parameters in a small study [90].

Ursodeoxycholic acid:

Ursodeoxycholic acid, a cytoprotective agent, used in nonalcoholic steatohepatitis showed promising result [91]. The combination of vitamin E and ursodeoxycholic acid results in some benefit.

The fibrosis in nonalcoholic fatty liver disease is induced by the renin-angiotensin system. Angiotensin-receptor blockers and Angiotensin-converting enzyme inhibitors improves the sensitivity of insulin. Treatment with ARBs showed improvement in liver histology.

Cardiovascular risk and lipid profile are improved by monounsaturated fatty acid. Polyunsaturated fatty acid improves liver function test and liver histology.

In nonalcoholic fatty liver disease, steatosis was improved by L-carnitine. The overgrowth of bacteria in the small intestine has been linked with the nonalcoholic fatty liver disease. This made us to use pre and probiotics in the treatment of non-alcoholic fatty liver disease. The relationship between consumption of coffee and nonalcoholic fatty liver disease is inverse. So we should recommend our patients to consume coffee at regular intervals.

Future trends in the treatment of nonalcoholic fatty liver disease are

1. Agents that inhibit TNF-α ,
2. Agents that increase levels of adiponectin,
3. Agents that alter levels of leptin
4. Agents that improve ATP homeostasis in mitochondria.

Liver Transplantation

Patients with nonalcoholic fatty liver disease with end-stage liver disease should be evaluated for liver transplantation. The outcome of liver transplantation in this nonalcoholic fatty liver disease is good. The nonalcoholic fatty liver disease can recur after liver transplantation [92, 93]. The risk factors for de novo or recurrent nonalcoholic fatty liver disease after liver transplantation probably are multifactorial and include diabetes mellitus, hypertriglyceridemia, glucocorticoid therapy, and obesity.

AIMS AND OBJECTIVES

AIM OF THE STUDY:

1. To clarify the characteristics of type 2 diabetic patients with non-alcoholic fatty liver disease (NAFLD).

2. To assess whether nonalcoholic fatty liver disease is related to diabetic micro and macroangiopathy.

METHODS AND MATERIALS

METHODS AND MATERIALS:

Study group **:** Patients with type2 diabetes mellitus who visited the Department Of Internal Medicine

Study design **:** Cross-Sectional study

Place of Study **:** Govt. Royapettah Hospital

Study population **: 100**

Duration of study **:** 6 months

Conflict of interest **: Nil.**

METHODOLOGY:

In patients with type 2 Diabetes Mellitus, Fasting & postprandial glucose, lipid profile, liver function test with enzymes, Ultrasonogram, Urine spot albumin creatinine ratio, ECG, Carotid Doppler for Carotid Intimal Thickness, Ankle brachial index by Oscillometric method, urea, and creatinine will be done after obtaining written informed consent and the findings correlated to find out whether NAFLD is an independent indicator of angiopathy in these patients.

The person weight is classified according to the Asian BMI chart as underweight, normal weight, overweight, and obese individual.

<18.5	Underweight
18.5 - 23.9	Healthy weight range
24 - 26.9	Overweight
>27	Obese

The peripheral arterial disease is diagnosed by using ankle brachial index. The ankle brachial index in diabetic patients is measured by oscillometry method. The peripheral arterial disease is classified into mild moderate and severe disease according to the following ankle brachial index values.

Severity (ABI value)
Mild (0.89–0.7)
Moderate (0.69–0.4)
Severe (<0.4)
Normal (>0.9)

Assessment and definition of diabetic nephropathy was based on the following criteria.

Diabetic nephropathy

(DN) was staged according to an analysis of the spot urine sample as:

“DN stage I (normoalbuminuria), albumin/creatinine ratio (ACR) <30 mg/g creatinine;

DN stage II (microalbuminuria): 30 _ACR <300 mg/g creatinine;

DN stage III (macroalbuminuria): ACR >300 mg/g creatinine and eGFR >30 mL/min/1.73m2;

DN stage IV: ACR _300 mg/g creatinine and eGFR <30 mL/min/1.73m2".

"**eGFR (mL/min/1.73m2)=194×Scr-1.094×Age-0.287×0.739"**

The patients' vibration senses are tested with 128 Hz turning fork. The peripheral neuropathy in diabetic patients is diagnosed by testing the vibration sense and deep tendon reflex. The fundus examination is done with direct ophthalmoscope by which diabetic retinopathy is identified. The ischemic heart disease is identified using electrocardiogram. The carotid intimal thickness is measured using Doppler ultrasound. The cerebrovascular accident is diagnosed by those having findings in the CT and those having TIA.

Inclusion criteria :

All patients with type 2 diabetes mellitus

Exclusion criteria:

1. Excessive alcohol ingestion

   (Consumption>21 drinks on average per week in men and >14 drinks on average per week, 1 alcoholic drink =10 grams of alcohol)

2. Wilson disease
3. Lipodystrophy
4. Starvation
5. Parenteral nutrition

6. Medications like amiodarone, methotrexate, tamoxifen, corticosteroids valproate, anti-retroviral medicines.

7. History of viral hepatitis, obesity related surgery

Data collection:

The data of each patient will be collected on a proforma specially designed for this study and which includes demographic details, clinical features, past medical history, clinical and Lab values which will be analyzed for statistical significance and correlation.

STATISTICAL ANALYSIS

Statistical analysis was done to identify significance and correlation between. Nonalcoholic fatty liver disease and diabetic micro and macroangiopathy Statistical analysis was done using Statistics Products Services Solutions (SPSS 15) software. Univariate analysis was done with paired t test and Pearson product moment correlation coefficient. A chi squared test was used to analyse the probability of differences in frequency distributions between the groups and $p<0.05$ was taken to be statistically significant in all calculations.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

PREVALANCE:

Table.7

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Yes	40	40.0	40.0	40.0
	No	60	60.0	60.0	100.0
	Total	100	100.0	100.0	

Table.7 shows the percentage of diabetic population having NAFLD.

According to our study the prevalence of nonalcoholic fatty liver disease in type 2 diabetes mellitus is 40%.

Chart.1

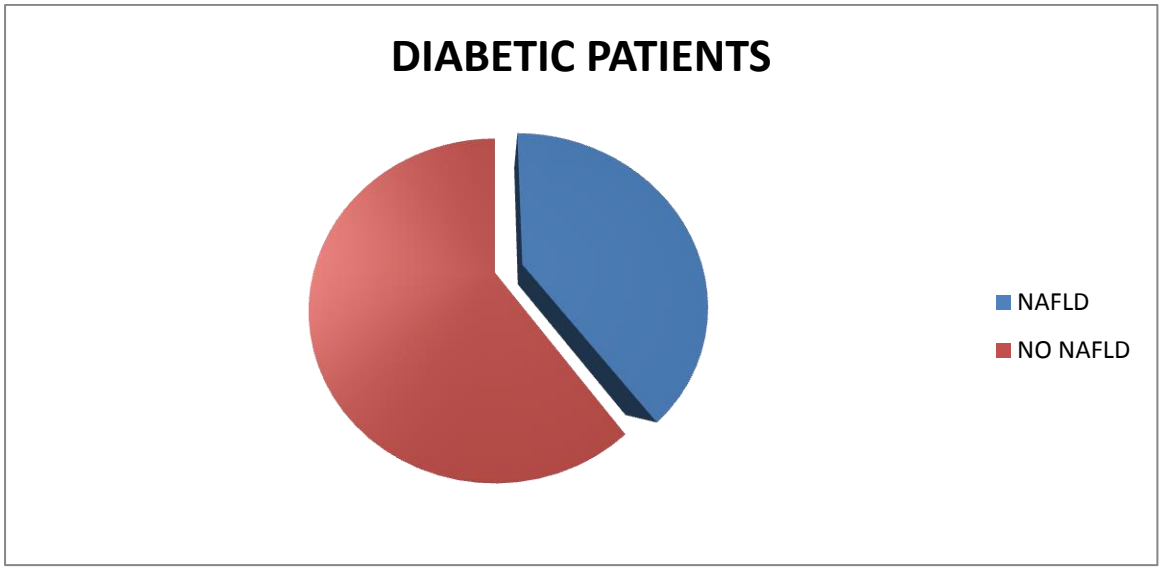


Chart.1 shows the percentage of diabetic population having NAFLD

Table . 8

			NAFLD		Total	P value
			Yes	No		0.281
Sex	Male	Count	19	22	41	
		% within Sex	46.3%	53.7%	100.0%	
		% within NAFLD	47.5%	36.7%	41.0%	
	Female	Count	21	38	59	
		% within Sex	35.6%	64.4%	100.0%	
		% within NAFLD	52.5%	63.3%	59.0%	
Total		Count	40	60	100	
		% within Sex	40.0%	60.0%	100.0%	
		% within NAFLD	100.0 %	100.0 %	100.0%	

Table .8 shows the sex distribution in patients with nonalcoholic fatty liver disease.

Out of 41 male patients with diabetes mellitus 19 had non-alcoholic fatty liver disease. Out of 59 female patients with diabetes mellitus 21 had non-alcoholic fatty liver disease with p value of .281which is statistically insignificant. So according to our study there is no gender difference in the incidence of nonalcoholic fatty liver disease in diabetes population.

Chart. 2

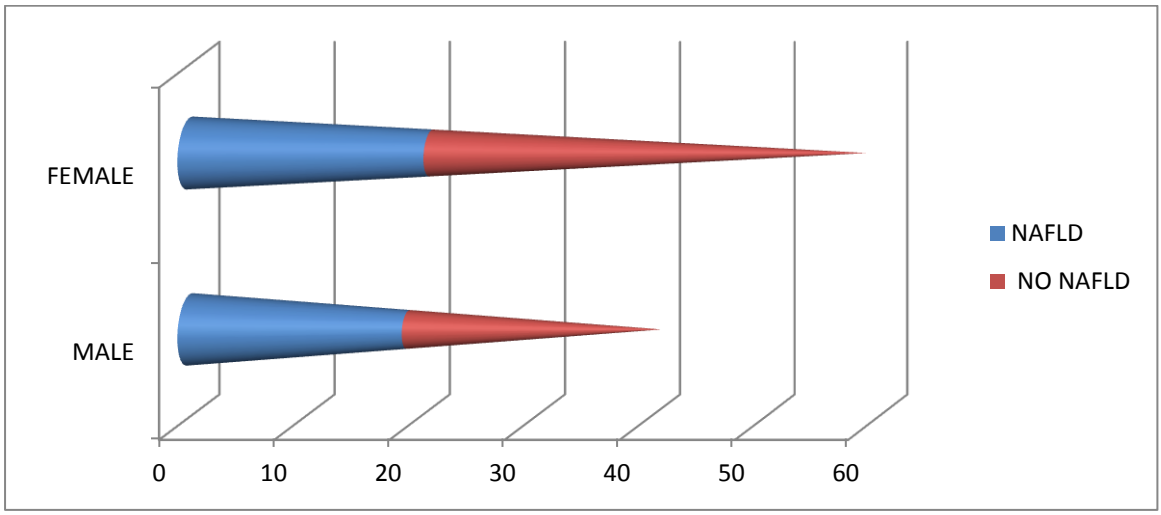


Chart.2 shows the sex distribution in patients with nonalcoholic fatty liver disease.

Chart.3

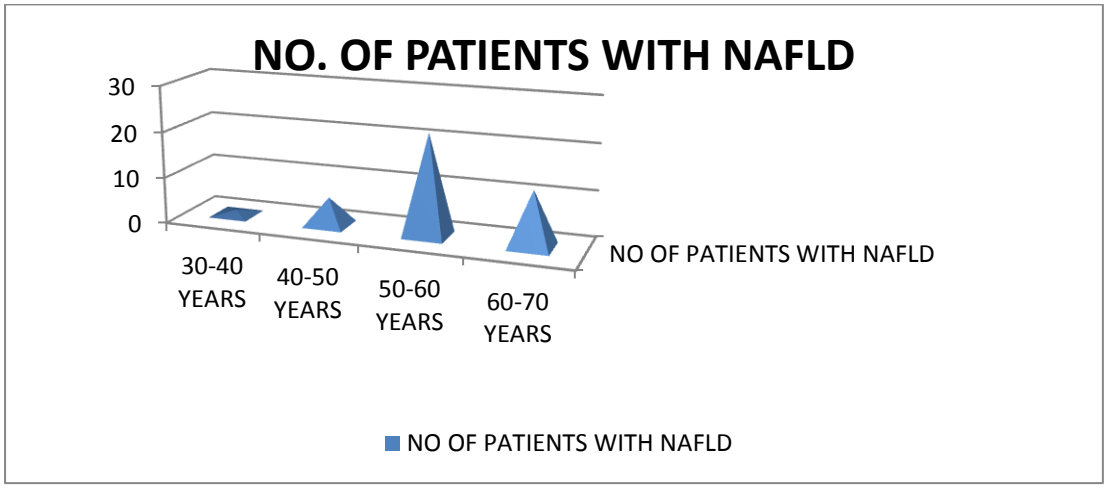


Chart.3 shows age distribution among nonalcoholic fatty liver disease.

Out of 40 patients with NAFLD 21 patients are in the age group of 50 to 60 years of age.

Table. 9

			NAFLD		Total	P value
			Yes	No		
BMI	Underweight	Count	1	0	1	0.001
		% within BMI	100.%	.0%	100.0%	
		% within NAFLD	2.5%	.0%	1.0%	
	Normal	Count	6	34	40	
		% within BMI	15.0%	85.0%	100.0%	
		% within NAFLD	15.0%	56.7%	40.0%	
	Over weight	Count	22	17	39	
		% within BMI	56.4%	43.6%	100.0%	
		% within NAFLD	55.0%	28.3%	39.0%	
	Obese	Count	11	9	20	
		% within BMI	55.0%	45.0%	100.0%	
		% within NAFLD	27.5%	15.0%	20.0%	
Total		Count	40	60	100	
		% within BMI	40.0%	60.0%	100.0%	
		% within NAFLD	100.0 %	100.0 %	100.0%	

Table.9 shows the weight distribution in diabetic patients having NAFLD and no NAFLD.

Out of 100 individual with type 2 diabetes mellitus,1 individual was underweight .40 person had normal weight ,39 person had overweight and 20 individual had obesity. Out 40 individual with NAFLD 1 had underweight, 6 person had normal weight, 22 person had overweight and 11 individual had obesity. So the patients with NAFLD are mostly obese and overweight which is statistically significant. (P value -0.001)

Chart. 4

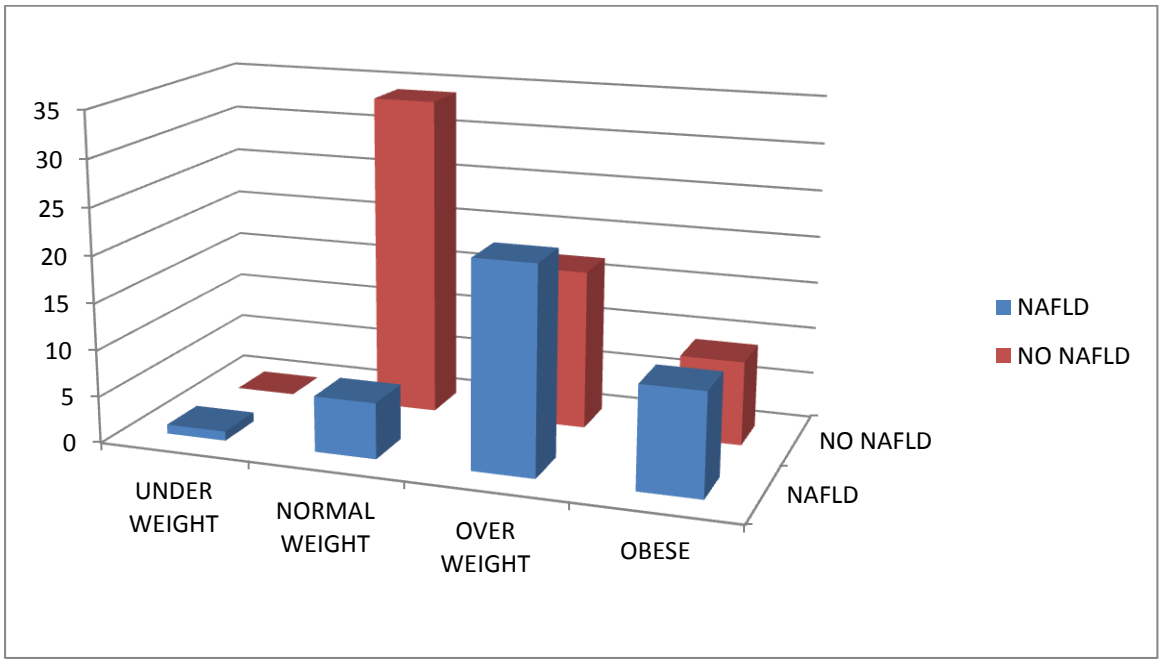


Chart 4 shows the weight distribution in diabetic patients having NAFLD and no NAFLD.

DURATION OF DIABETES

Table.10

	NAFLD	N	Mean	Std. Deviation	Std. Error Mean	P value
Duration of Diabetes	Yes	40	4.50	2.013	.318	0.062
	No	60	3.82	2.087	.269	

Table. 10.shows the duration of diabetes in NAFLD and no NAFLD patients. The mean duration of diabetes in NAFLD group is 4.5years and the mean duration of years in no NAFLD group was 3.82 which is statistically insignificant. (P value -0.062)

BLOOD PRESSURE

TABLE.11

	NAFLD	N	Mean	Std. Deviation	Std. Error Mean	P value
SBP	Yes	40	139.95	15.100	2.387	0.006
	No	60	129.93	18.966	2.449	
DBP	Yes	40	88.53	11.602	1.834	0.012
	No	60	82.95	9.989	1.290	

Table .11 shows mean blood pressure in diabetic NAFLD patients.

The mean systolic blood pressure of NAFLD group was 139.95 and that of no NAFLD group was 129.93. The mean diastolic blood pressure of NAFLD group was 88.53and that of no NAFLD group was 82.95.So the patients with NAFLD have high systolic and diastolic blood pressure which is statistically significant (p value -0.006 and 0.012)

PERIPHERAL ARTERIAL DISEASE

Table.12

			NAFLD		Total	P value
			Yes	No		
ABI	Normal	Count	26	41	67	0.692
		% within ABI	38.8%	61.2%	100.0%	
		% within NAFLD	65.0%	68.3%	67.0%	
	Mild	Count	11	12	23	
		% within ABI	47.8%	52.2%	100.0%	
		% within NAFLD	27.5%	20.0%	23.0%	
	Moderate	Count	2	6	8	
		% within ABI	25.0%	75.0%	100.0%	
		% within NAFLD	5.0%	10.0%	8.0%	
	Severe	Count	1	1	2	
		% within ABI	50.0%	50.0%	100.0%	
		% within NAFLD	2.5%	1.7%	2.0%	
Total		Count	40	60	100	
		% within ABI	40.0%	60%	100%	
		% within NAFLD	100.0%	100.0%	100.0%	

Table.12 shows the ankle brachial index distribution in diabetic patients having NAFLD and no NAFLD.

Among 100 diabetic patients 33 patients had peripheral arterial disease. Among 33 patients with peripheral arterial disease 23 had mild disease 8 had moderate disease 2 had severe disease. Among NAFLD patients 11 had mild disease 2 had moderate disease 1 had severe disease. Out of 40 patients with NAFLD 14 patients had peripheral arterial disease. The prevalence of peripheral arterial disease among diabetic patients with NAFLD is not high when compared to that of no NAFLD diabetic group (14 vs 19) and it is statistically insignificant (P value 0.692).

Chart.5

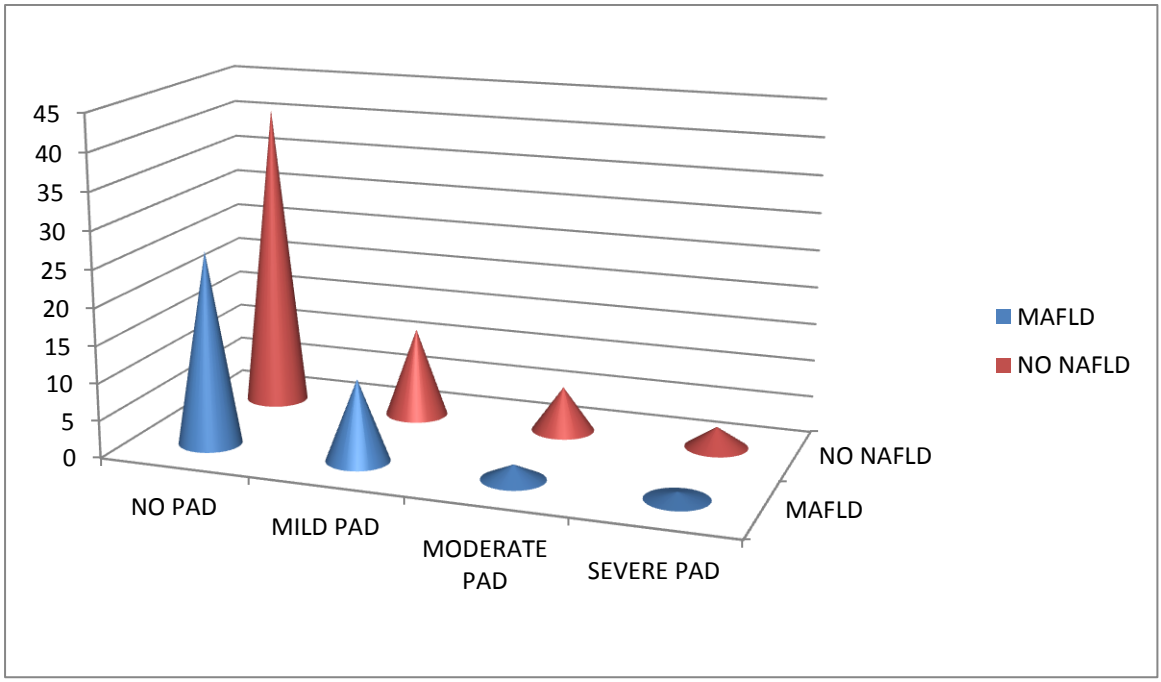


Chart.5 shows the ankle brachial index distribution in diabetic patients having NAFLD and no NAFLD.

CEREBROVASCULAR ACCIDENT

Table.15

			NAFLD		Total	P value
			Yes	No		
CVA	Yes	Count	10	2	12	0.001
		% within CVA	83.3%	16.7%	100.0%	
		% within NAFLD	25.0%	3.3%	12.0%	
	No	Count	30	58	88	
		% within CVA	34.1%	65.9%	100.0%	
		% within NAFLD	75.0%	96.7%	88.0%	
Total		Count	40	60	100	
		% within CVA	40.0%	60.0%	100.0%	
		% within NAFLD	100.0%	100.0%	100.0%	

Table.15 shows the CVA distribution in diabetic patients having NAFLD and no NAFLD.

Out of 100 patients with diabetes 12 patients had cerebrovascular accident. Out of 40 patients with NAFLD 10 had cerebrovascular accident and 30 did not have cerebrovascular accident. So prevalence of cerebrovascular accident is high among NAFLD diabetic patients when compared to that of no NAFLD diabetic group (10 vs 2) which is statistically significant (p value -.001)

Chart.8

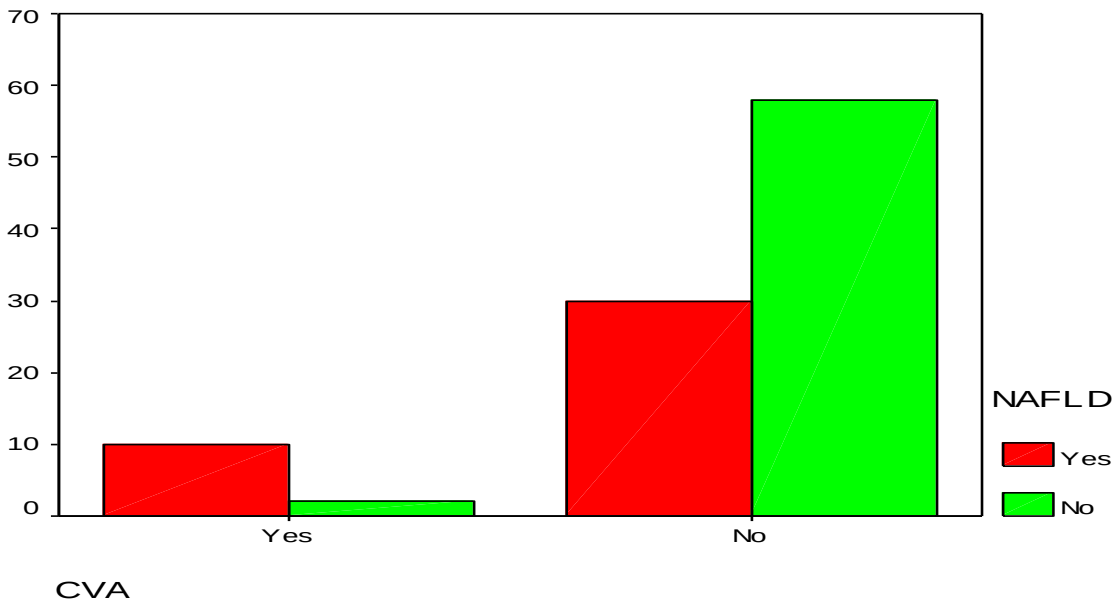


Chart.8 shows the CVA distribution in diabetic patients having NAFLD and no NAFLD.

ISCHEMIC HEART DISEASE

Table.16

			NAFLD		Total	P value
			Yes	No		
IHD	Yes	Count	18	12	30	.008
		% within IHD	60.0%	40.0%	100.0%	
		% within NAFLD	45.0%	20.0%	30.0%	
	No	Count	22	48	70	
		% within IHD	31.4%	68.6%	100.0%	
		% within NAFLD	55.0%	80.0%	70.0%	
Total		Count	40	60	100	
		% within IHD	40.0%	60.0%	100.0%	
		% within NAFLD	100.0%	100.0%	100.0%	

Table.16 shows the ischemic heart disease distribution in diabetic patients having NAFLD and no NAFLD.

Out of 100 patients with diabetes 30 patients had ischemic heart disease. Out of 40 patients with NAFLD 18 had ischemic heart disease and 12 did not have ischemic heart disease. Out of 30patients with ischemic heart disease 18 had NAFLD. So prevalence of ischemic heart disease is high among NAFLD diabetic patients when compared to that of no NAFLD diabetic group(18 vs 12) which is statistically significant (p value -0.008).

Chart.9

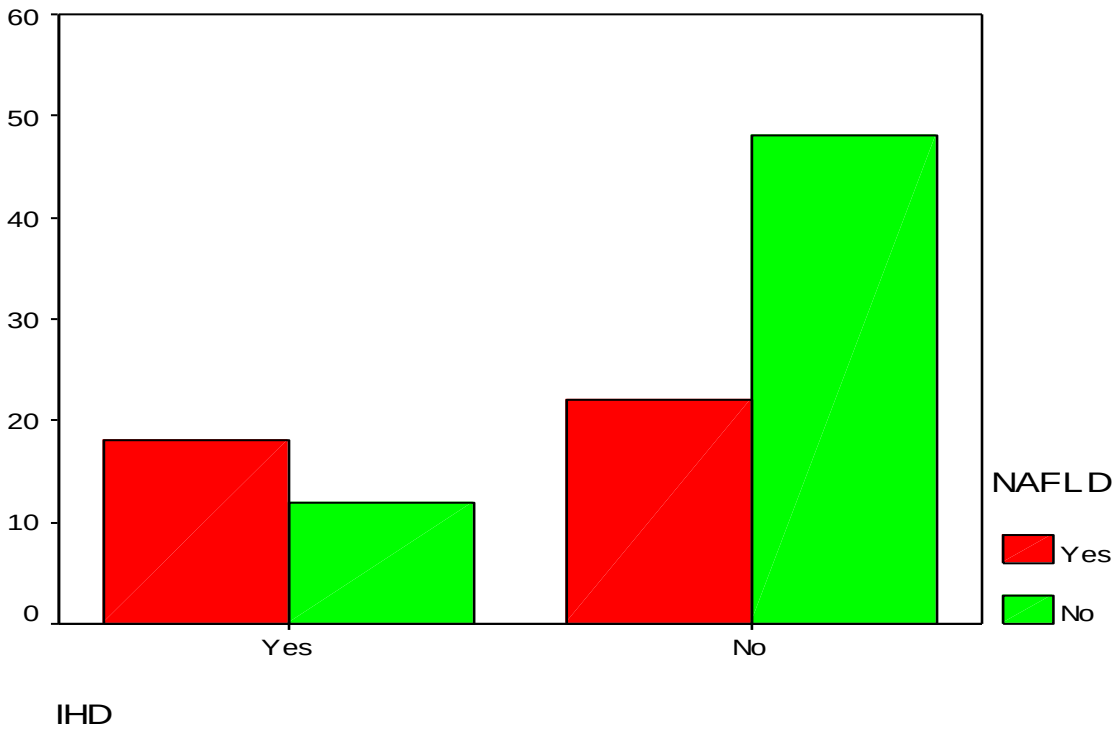


Chart.9 shows the ischemic heart disease distribution in diabetic patients having NAFLD and no NAFLD

CAROTID INTIMAL MEDIAL THICKNESS

Table.17

	NAFLD	N	Mean	Std. Deviation	Std. Error Mean	p value
CIMT	Yes	40	.789	.1961	.0310	.010
	No	60	.698	.1489	.0192	

Table.17 shows the mean carotid intimal medial thickness.

The mean carotid intimal medial thickness in NAFLD group is.789 and that of no NAFLD group is 0.698. So the intimal medial thickness is high in NAFLD group which is statistically significant (P 0.010).

RETINOPATHY:

Table.13

			NAFLD		Total	P value
			Yes	No		0.001
RETINOPATHY	Yes	Count	17	7	24	
		% within Retinopathy	70.8%	29.2%	100.0%	
		% within NAFLD	42.5%	11.7%	24.0%	
	No	Count	23	53	76	
		% within Retinopathy	30.3%	69.7%	100.0%	
		% within NAFLD	57.5%	88.3%	76.0%	
Total		Count	40	60	100	
		% within Retinopathy	40.0%	60.0%	100.0%	
		% within NAFLD	100.0%	100.0 %	100.0%	

Table.13 shows the retinopathy distribution in diabetic patients having NAFLD and no NAFLD.

Out of 100 patients with diabetes 24 patients had retinopathy. Out of 40 patients with NAFLD 17 had retinopathy and 23 did not have retinopathy. So prevalence of retinopathy is high among NAFLD diabetic patients when compared to that of no NAFLD diabetic group (17 vs 7) which is statistically significant. (p value -0.001)

Chart: 6

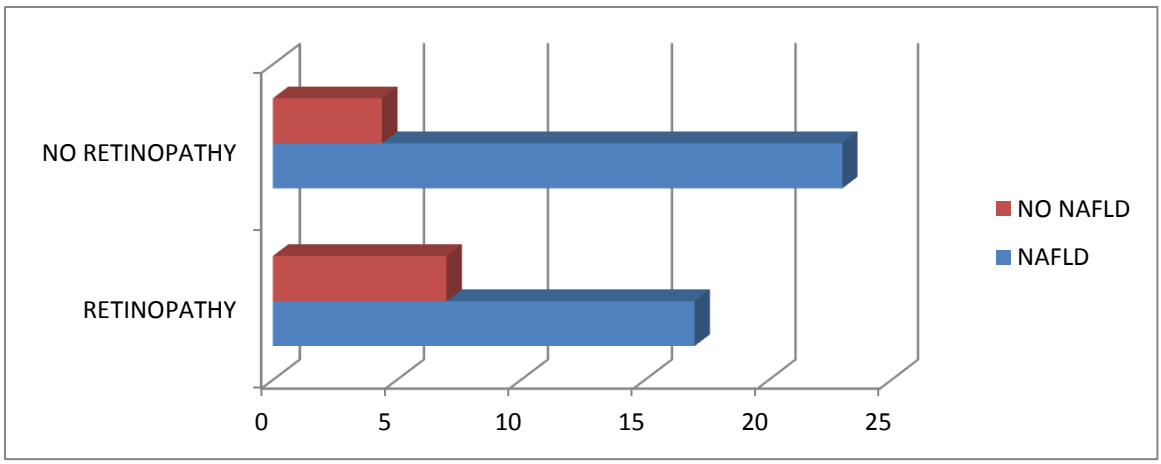


Chart.6 shows the retinopathy distribution in diabetic patients having NAFLD and no NAFLD.

PERIPHERAL NEUROPATHY

Table.14

			NAFLD		Total	P value
			Yes	No		
Peripheral Neuropathy	Yes	Count	18	0	18	< 0.001
		% within Neuropathy	100.0%	.0%	100.0%	
		% within NAFLD	45.0%	.0%	18.0%	
	No	Count	22	60	82	
		% within Neuropathy	26.8%	73.2%	100.0%	
		% within NAFLD	55.0%	100.0%	82.0%	
Total		Count	40	60	100	
		% within Neuropathy	40.0%	60.0%	100.0%	
		% within NAFLD	100.0%	100.0%	100.0%	

Table.14 shows the peripheral neuropathy distribution in diabetic patients having NAFLD and no NAFLD.

Out of 100 patients with diabetes 18 patients had peripheral neuropathy. Out of

40 patients with NAFLD, 18 had peripheral neuropathy and 22 did not have

peripheral neuropathy. The prevalence of peripheral neuropathy among no NAFLD group is 0. All 18 patients with peripheral neuropathy had NAFLD. So in our study the prevalence of peripheral neuropathy is high among NAFLD diabetic patients when compared to that of no NAFLD diabetic group(18 vs 0) which is statistically significant (p value -.001).

Chart.7

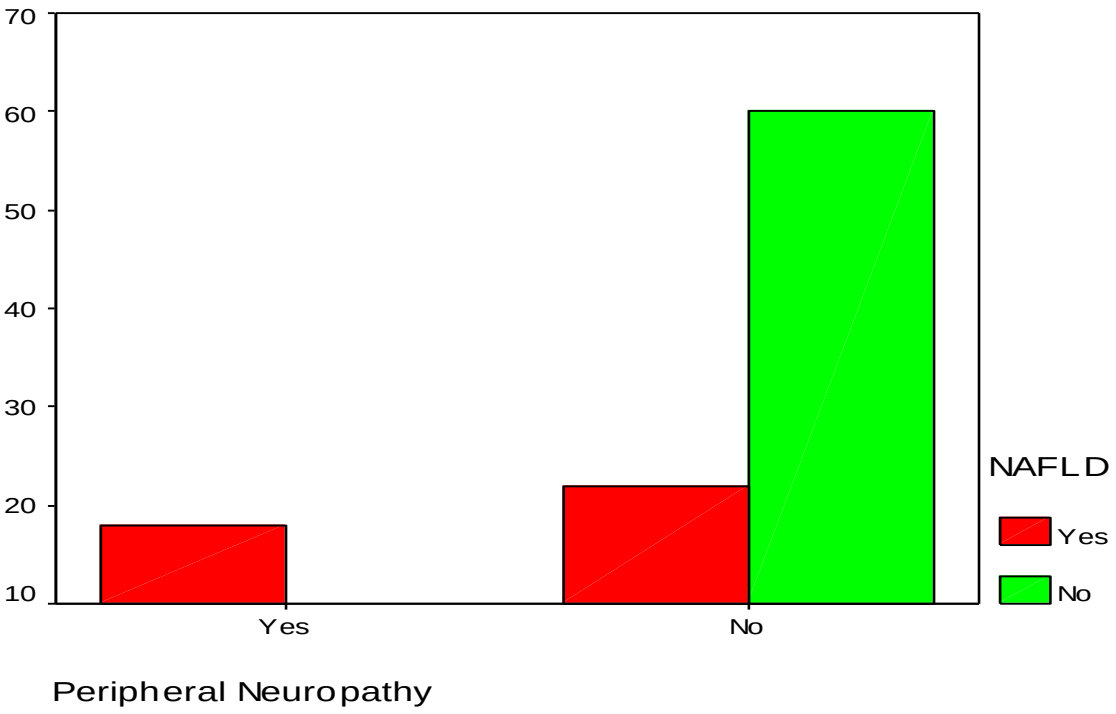


Chart.7 shows the peripheral neuropathy distribution in diabetic patients having NAFLD and no NAFLD.

Diabetic nephropathy (DN)

Table.18

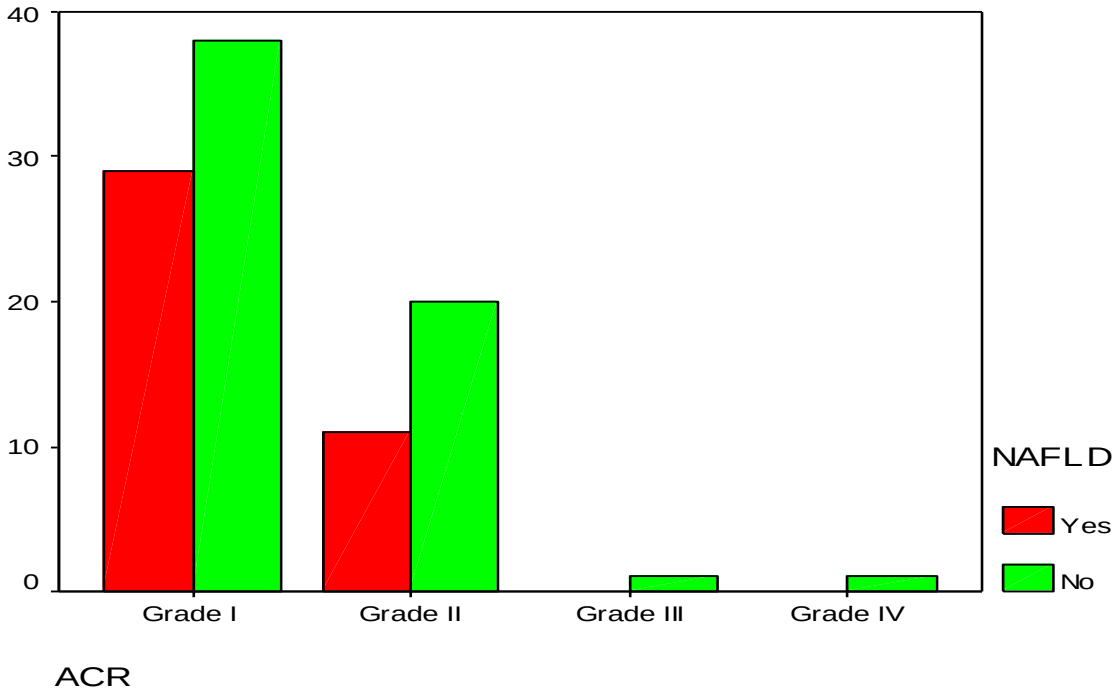
			NAFLD		Total	P value
Diabetic nephropathy (DN)			Yes	No		
	Grade I	Count	29	38	67	0.594
		% within DN	43.3%	56.7%	100.0%	
		% within NAFLD	72.5%	63.3%	67.0%	
	Grade II	Count	11	20	31	
		% within DN	35.5%	64.5%	100.0%	
		% within NAFLD	27.5%	33.3%	31.0%	
	Grade III	Count	0	1	1	
		% within DN	.0%	100.0%	100.0%	
		% within NAFLD	.0%	1.7%	1.0%	
	Grade IV	Count	0	1	1	
		% within DN	.0%	100.0%	100.0%	
		% within NAFLD	.0%	1.7%	1.0%	
Total		Count	40	60	100	
		% within DN	40.0%	60.0%	100.0%	
		% within NAFLD	100.0%	100.0%	100.0%	

Table.18 shows the diabetic nephropathy distribution in diabetic patients having NAFLD and no NAFLD

Out of 100 patients with diabetes 67 patients are in grade 1 diabetic nephropathy, 31 patients are in grade 2 diabetic nephropathy, 1 patient is in grade 3 diabetic nephropathy,1 patient is grade 4 diabetic nephropathy.

Out of 40 diabetic patients with NAFLD 29 patients are in grade 1 diabetic nephropathy, 11 patients are in grade 2diabetic nephropathy and there is no patient in grade 3 and grade 4nephropathy.

There is no co relation between NAFLD and diabetic nephropathy and it is

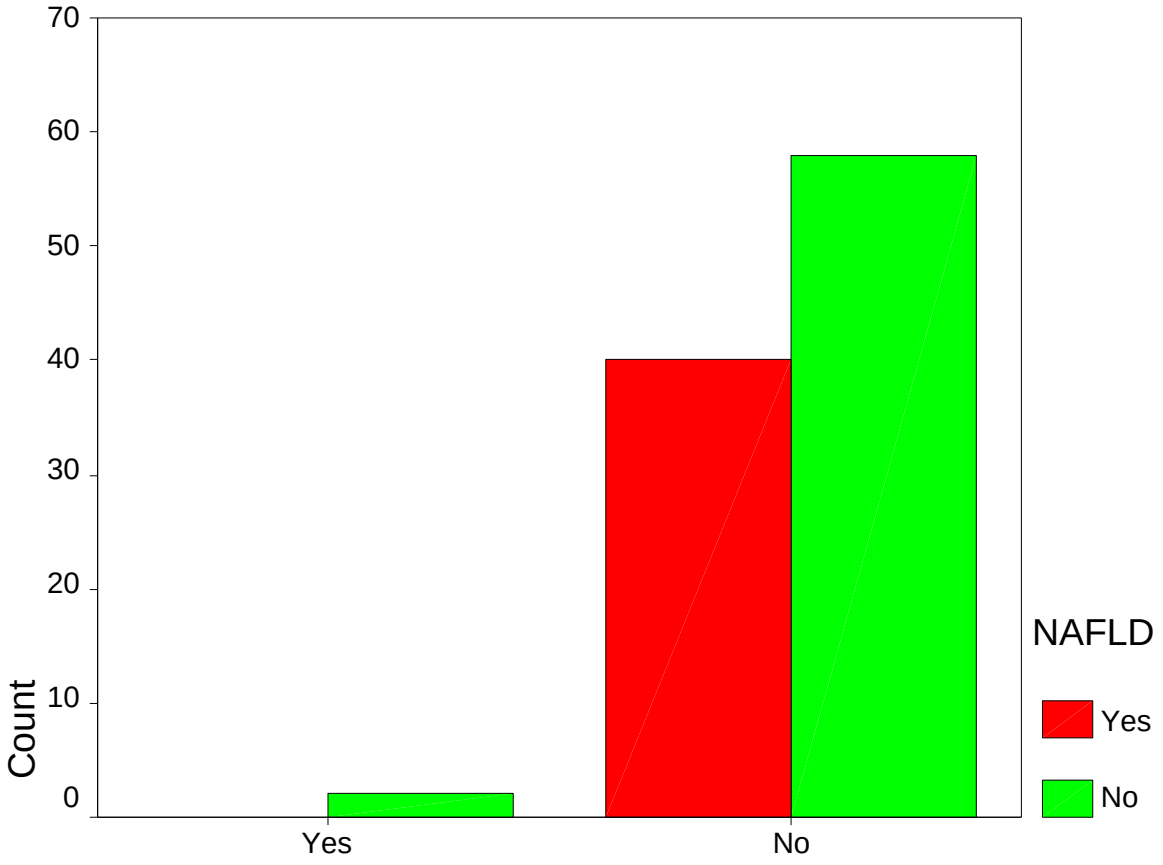


statistically insignificant. (p value-0.594)

GFR LESS THAN 30

			NAFLD		Total	P value
			Yes	No		
GFR < 30	Yes	Count	0	2	2	0.243
		% within < 30	.0%	100.0%	100.0%	
		% within NAFLD	.0%	3.3%	2.0%	
	No	Count	40	58	98	
		% within GFR <30	40.8%	59.2%	100.0%	
		% within NAFLD	100.0%	96.7%	98.0%	
Total		Count	40	60	100	
		% within GFR <30	40.0%	60.0%	100.0%	
		% within NAFLD	100.0%	100.0%	100.0%	

Out of 100 patients with diabetes only 2 had GFR less than 30. In our study none of the NAFLD diabetic patients had GFR less than 30 and it is statistically insignificant (p value-0.243).



Group Statistics

	NAFLD	N	Mean	Std. Deviation	Std. Error Mean	p value
Age in years	Yes	40	56.98	7.694	1.217	.062
	No	60	54.37	6.065	.783	
Duration of Diabetes	Yes	40	4.50	2.013	.318	.107
	No	60	3.82	2.087	.269	
SBP	Yes	40	139.95	15.100	2.387	.006
	No	60	129.93	18.966	2.449	
DBP	Yes	40	88.53	11.602	1.834	.012
	No	60	82.95	9.989	1.290	
Fasting sugar	Yes	40	115.70	34.187	5.405	.673
	No	60	118.67	34.345	4.434	
Post Prandial Sugar	Yes	40	165.95	34.809	5.504	.988
	No	60	165.85	33.023	4.263	
UREA	Yes	40	32.63	9.080	1.436	.049
	No	60	38.28	16.306	2.105	
Creatinine	Yes	40	.880	.2441	.0386	.189
	No	60	.983	.4514	.0583	
Triglycerides	Yes	40	182.98	40.972	6.478	<.001
	No	60	157.05	27.567	3.559	
Total Cholesterol	Yes	40	238.63	31.181	4.930	.028
	No	60	232.60	32.941	4.253	
ABI	Yes	40	.916	.2161	.0342	0.865
	No	60	.908	.1992	.0257	
CIMT	Yes	40	.789	.1961	.0310	.010
	No	60	.698	.1489	.0192	
AST	Yes	40	42.63	24.147	3.818	.115
	No	60	37.45	6.060	.782	
ALT	Yes	40	47.68	38.090	6.023	.049
	No	60	37.80	4.804	.620	
Total Protein	Yes	40	6.9900	.41928	.06629	.684
	No	60	7.0267	.45206	.05836	
Albumin	Yes	40	3.9200	.42740	.06758	.389
	No	60	4.0017	.48380	.06246	

DISCUSSION

DISCUSSION

Nowadays the prevalence of nonalcoholic liver disease is raising in the general population especially those with diabetes, metabolic syndrome, and obese individual. There is geographic variation in the prevalence of nonalcoholic liver disease.

PREVALENCE:

The prevalence of nonalcoholic liver disease in the type 2 diabetic population in government Royapettah hospital is 40%.According to one study in type 2 diabetes mellitus which is conducted in north India which used liver histology in the diagnosis of non-alcoholic liver disease, the prevalence of non-alcoholic liver disease was 88%,the prevalence of NASH was 63%,the prevalence of fibrosis was 38%[94]. In our study the prevalence of nonalcoholic liver disease was made using imaging modality as per definition of AASLD. According to **Schwenzen et al** the sensitivity and specificity of ultrasound in making the diagnosis of nonalcoholic liver disease was up to 94%and upto 95% respectively [95]. According to the study conducted by **Browning J et al** diabetic patients concomitantly had NAFLD upto 45% of the cases [96, 97, 98] According to **Bellentani et al** the prevalence of non-alcoholic liver disease among type 2 diabetes mellitus was 30 to 50% [99].

AGE AND SEX:

According to our study the prevalence of non-alcoholic liver disease among type 2 diabetes patients was high in the 50 to 60 years age group. According to **Bellentai et al** the prevalence and the severity of nonalcoholic liver disease increases with increasing age [100]. **According to Hu X et al** Older age, male gender are the risk factors in the development of NAFLD [101].

According to the study conducted by **Hilden m et al** the prevalence of nonalcoholic liver disease in the individuals below 20 years was 1%, between 20 to 40 years was 18%,and 60 and more years was 39%.

According to our study there is no sex difference in the prevalence of nonalcoholic liver disease(male vs female 19 vs 21).According to the study conducted by **Sheth et al** the prevalence of nonalcoholic liver disease was high among women[102].

According to the study conducted by **Caruli et al** the prevalence of nonalcoholic liver disease was high among men[103].This is because female are protected against non-alcoholic liver disease by female sex hormones[104].The gender difference in the prevalence of non-alcoholic liver disease may be due to the difference in the distribution of fat among women[105, 106].

BODY MASS INDEX:

According to our study obese individuals and overweight individuals had high frequency of getting NAFLD when compared with that of normal weight individuals(11vs 9 obese individual,22vs 17 overweight individual).According to **Jokoben M U et al** the prevalence of NAFLD is high among those patients having high BMI and those having high waist circumference[107]. According to **Dionysos study** the NAFLD was present in 94% of the obese individuals, 67% of the overweight individual.

According to **Angulo p et al** the obese individuals are having high frequency of getting NAFLD and will have the severe form of disease [108]. According to our study in patients having NAFLD 55% are overweight, 27.5% are obese,15% are normal weight and 2.5% are under weight. According to our study the mean duration of diabetes in NAFLD patients is 4.5 years and those not having NAFLD were 3.82 years.

According to the study conducted by **Vishwanathan et al** which is conducted in south India the mean duration of diabetes in NAFLD group was 9 years [109]. According to **LvWS et al** NAFLD negatively correlated with the duration of diabetes[110].

BLOOD PRESSURE:

According to our study the patients with NAFLD had both high systolic and high diastolic blood pressure when compared to that of those not having NAFLD (systolic bp140 vs130). According to **Luminita et al** the prevalence of NAFLD was very high in the nondipper, reverse dipper, and extreme dipper than those who were dipper. NAFLD and hypertension are correlated because of insulin resistance which is involved in the pathogenesis of both the diseases. According to this study altered BP level is a marker of NAFLD [111].

According to **Lv WS et al** patients with NAFLD had greater body weight, fasting blood glucose (FBG), , blood pressure ,concentration than those without NAFLD ($P < 0.05$).[110]

BLOOD GLUCOSE LEVELS:

According to our study there is no correlation between blood sugar level and NAFLD group and the mean fasting blood glucose level of NAFLD group and no NAFLD group was 115.70 vs 118.67 mean postprandial blood glucose level of NAFLD group and no NAFLD group 165.95 vs 165.85.

According to **Jimba et al** the prevalence of NAFLD is high among the individuals having high blood sugar in general population [112].

According to **S.Bajaj et al** the diabetic patients who are having NAFLD had high fasting blood sugar and insulin level [113].

According to the study conducted by **Saint Loius university**, accumulation of fat in the liver occurs as a result of resistance to insulin in NAFLD individuals. In NAFLD because of resistance to insulin, body cell reacts poorly to the insulin which causes hyperglycemia [114].

DYSLIPIDEMIA:

According to our study the diabetic NAFLD patient had high total cholesterol and high triglycerides level than compared with no NAFLD patients which are statistically significant. The mean TGL and Total cholesterol were 182.98 vs 157.05, and 238.63 vs 233.37 in NAFLD and no NAFLD patients. So dyslipidaemic individuals are at high risk of getting NAFLD.

According to **Chatrath H et al** NAFLD individuals often had altered lipid metabolism along with the characteristics of metabolic syndrome. The NAFLD individual usually will have increased triglycerides, "increased LDL (nontype A) particles and decreased HDL" .The altered lipid metabolism in NAFLD is due to overproduction VLDL by the liver and decreased clearance of lipid by the liver [115].

According to **David e cohen** NAFLD usually has an atherogenic lipid profile. The pathogenesis of atherogenic lipid profile in NAFLD is due to insulin resistance [116].

SERUM ALBUMIN LEVEL:

In our study the mean albumin in NAFLD and no NAFLD group was 3.92 vs 4.00.Even though the NAFLD patients had low albumin than no NAFLD group, there was no statistical significance. According to **Younossi ZM et al** high bilirubin, low albumin and increased prothrombin time are the predictor's of mortality in NAFLD patients [117].

According to **Fierbinteanu-Braticevici et al** CRP, splenic longitudinal diameter, insulin resistance scale, GGT, INR, age, body mass index, albumin are correlated well with NASH. The four predictors of NASH are "CRP (p=0.004), SLD (p=0.018), HOMA (p=0.03) and albumin level (p=0.041)".the albumin (p=0.008), is associated with severe fibrosis [118].

TRANSAMINASES LEVELS:

In our study out of 100 patients only 3 patients had transaminase elevation. The elevation of ALT is statistically significant in NAFLD patients when compared with that of no NAFLD patients. There is no correlation between NAFLD and AST levels.

A study was conducted by **Ioannou et al** based on 10 year risk of cardiovascular events by Framingham risk score (FRS) in individuals with elevated and normal ALT levels. The ALT is said to be elevated when it is more

than 43 IU/L. According to this study the elevated ALT are associated with high FRS score [119].

According to a **Swedish study** there was increased mortality in patients with NAFLD who had elevated liver enzyme level. The level of enzyme in NAFLD patients may be normal [120].Among NAFLD individuals usually there will be fluctuation of liver enzymes [121].

ALT level varies according to the severity of liver steatosis than GGT levels [122].According to **Kotronen A et al** the elevated level ALT correlate with increased cardiovascular mortality.[123,124,125]. According to **Yun KE et al** the correlation between ALT level and CV mortality is mainly due to insulin resistance, which is strong risk factor for both diseases. [126]

PERIPHERAL ARTERIAL DISEASE:

According to our study there is no relationship between NAFLD and the peripheral arterial disease among diabetic paopulation. In our study the peripheral arterial disease was diagnosed by using Oscillometric method. According to **AM MacDougall et al** the sensitivity and the specificity of oscillometry in establishing the diagnosis of peripheral arterial disease was 71% and 89% [127].

According to the study conducted by **Yucihiro et al** there is no relationship between NAFLD and PAD [128]. This study was conducted in japan.

A large study conducted in south India by **Vishwanathan et al** found that there is no correlation between NAFLD and PAD among diabetic population. [109]

CAROTID INTIMAL MEDIAL THICKNESS:

According to our study mean carotid intimal medial thickness was high in patients with NAFLD than those without NAFLD. The mean CIMT between NAFLD and no NAFLD group was 0.789 Vs 0.698 .The no NAFLD patients had lower CIMT than NAFLD patients. So there is positive correlation between CIMT and NAFLD.

A study in Italy conducted by ***Pacifico L et al*** *in* paediatric population showed that carotid artery intima-media thickness (IMT) was high in NAFLD obese children than those obese children without NAFLD and lean children [131].

According to **Vishwanathan et al** there is a positive correlation between NAFLD and CIMT. [109]. According to **Yuchirio et al**, NAFLD patients who are in advanced age had higher CIMT than those without NAFLD in diabetic patients. [128]

A study conducted by **Targher at al** showed there is correlation between the CIMT and the histological severity of NAFLD [122].

ISCHEMIC HEART DISEASE:

According to our study the prevalence of ischemic heart disease is high among diabetic NAFLD patients.60% of patient with ischemic heart disease had NAFLD.

A study conducted in 129 patients with NAFLD in **Sweden** showed a high incidence of cardiovascular mortality in NAFLD patients when compared with that of general population. [132]

A study conducted in turkey by **Arslan U** with 92 individuals who had undergone coronary angiography, showed that NAFLD increased the risk of coronary artery disease as shown by coronary angiogram [133].

The study conducted by **Targher G et** al showed increased prevalence of IHD (22 % vs. 15%), CVA (17% vs. 10%) and PAD (13% vs. 7%) in people with type2 diabetes with NAFLD [129].

According to **ATP 3 panel** NAFLD patients had risk factors that may accentuate atherosclerosis. ATP 3 panel suspected that the NAFLD individuals are at maximum risk of getting ischemic heart disease [134].

In United States it was found that the prevalence of obesity and metabolic syndrome are increasing which is a common risk factor for both NAFLD and ischemic heart disease [135-137].

The patients with NAFLD who had high degree of inflammation and fibrosis had elevated levels of CRP and IL6 [138] .So NAFLD is considered as a chronic inflammatory condition which may accelerate atherosclerosis.

The levels of adiponectin antiatherogenic cytokines are reduced in NAFLD, which may explain the mechanism of accelerated atherosclerosis [139].

According to **Dunn W at el** who conducted study in 1000 NAFLD patients with the control of 6600 patients. All of them were followed for a mean duration of 9 years. This study showed that NAFLD patients had increased mortality due to cardiovascular diseases mainly around the age of 50 years [140] .

A study was conducted with type 1 diabetes mellitus **by Targher G et al** showed that there is high prevalence of cardiovascular death in the NAFLD patients[141].

In **Verona study** it was found that diabetic cirrhosis patients die mainly due cardiovascular complication when compared with that of general population **("standardized mortality ratio"=1.34) [142].**

CEREBROVASCULAR ACCIDENT

In our study there is positive correlation between NAFLD diabetic patients with Cerebrovascular accident. There is high prevalence of NAFLD in the stroke patients.

The study conducted by **Targher G et** al showed increased prevalence of IHD (22 % vs. 15%), CVA (17% vs. 10%) and PAD (13% vs. 7%) in people with type2 diabetes with NAFLD [129].

DIABETIC NEPHROPATHY

According to our study there is no correlation between albuminuria and NAFLD in the diabetic patients. The no NAFLD group had severe forms of diabetic nephropathy namely stage 3 and stage 4 nephropathy.

According to the study conducted by **Yucihiro et al** there is no relationship between NAFLD and diabetic nephropathy among diabetic population [128]. This study was conducted in japan.

A large study conducted in south India by **Vishwanathan et al** found that there is no correlation between NAFLD and diabetic nephropathy among diabetic population. [109]

According to the study conducted by **Hwang ST et al** there is very good relationship between NAFLD and microalbuminuria and newly detected diabetes and with prediabetes [143].

DIABETIC NEUROPATHY

According to our study there is a very strong correlation between NAFLD diabetic patients and peripheral neuropathy. In our study all patients with peripheral neuropathy had NAFLD.

According to **Yuichiro Takeuchi et al** there is no correlation between NAFLD and neuropathy [128]. According to **Vishwanathan et al** who conducted study in south India there is a strong correlation between NAFLD and neuropathy [109].

According to study conducted by **Lv WS et al** negatively correlated diabetic retinopathy and diabetic neuropathy with NAFLD patients [90].

DIABETIC RETINOPATHY

According to our study there is a strong correlation between NAFLD and diabetic retinopathy. According to **LvWS et al** NAFLD negatively correlated with diabetic retinopathy [110]. According to **Targher G, Bertolini L** who conducted studies in type 1 diabetes mellitus, diabetic NAFLD patients had high prevalence of CKD and retinopathy [145].

According to **Yuichiro Takeuchi et al** there is no correlation between NAFLD and retinopathy [128]. According to **Vishwanathan et al** who conducted study in south India there is strong correlation between NAFLD and retinopathy.[109].

According to study conducted in type 2 diabetes mellitus **by Targher G, Bertolini L et al** the prevalence of chronic kidney disease and diabetic retinopathy is high among NAFLD individuals [144].

LIMITATIONS OF THE STUDY

1. Sample size was small so further studies with bigger sample size has to be done to further verify the results.
2. Our study has been done among the population attending Government Royapettah hospital OPD and there can be a bias in selecting such a group of population, so this study has to be done among the general population or it has been done at multiple centers and meta-analysis of those studies can provide a significant conclusion of this issue.

CONCLUSION

CONCLUSION

1. The diabetic patients with nonalcoholic liver disease are mostly overweight and obese.

2. The diabetic patients with nonalcoholic liver disease are mostly in the age group of 50 to 60 years of age.

3. The diabetic patients with nonalcoholic liver disease have high triglyceride level and high total cholesterol level.

4. The diabetic patients with nonalcoholic liver disease have both high systolic and diastolic blood pressure.

5. The diabetic patients with nonalcoholic liver disease had high prevalence of ischemic heart disease.

6. The diabetic patients with nonalcoholic liver disease had high prevalence of diabetic retinopathy.

7. The diabetic patients with nonalcoholic liver disease had high prevalence of diabetic peripheral neuropathy.

8. The diabetic patients with nonalcoholic liver disease had a high prevalence of cerebrovascular accident and have increased carotid intimal medial thickness.

9. The diabetic patients with nonalcoholic liver disease did not have any relation with diabetic nephropathy and peripheral arterial disease.

Thus NAFLD in type 2 diabetes mellitus independently predicts of diabetic microangiopathy and diabetic macroangiopathy and the characteristics of NAFLD in type 2 diabetes mellitus are studied.

DISCLOSURE

The investigator has not received any form of grants or support from any institution or pharmaceutical company.

APPENDIX

ABBREVIATIONS

NAFLD Nonalcoholic Fatty Liver Disease

CKD Chronic Kidney Disease

ACR Albumin Creatinine Ratio

CIMT Carotid Intimal Medial Thickness

IHD Ischemic Heart Disease

CVA Cerebrovascular Accident

BMI Body Mass Index

PAD Peripheral Arterial Disease

DN Diabetic Nephropathy

DR Diabetic Retinopathy

TGL Triglycerides

ABI Ankle Brachial Index

ATP 3 Adult Treatment Panel 3

GFR Glomerular Filtration Rate

PROFORMA

NAME:

AGE:

SEX:

ADDRESS:

HISTORY:

h/o of bilateral spontaneous pain, hypoesthesia Paraesthesia

h/o of previous myocardial infarction

h/o systemic hypertension

h/o chronic kidney disease

h/o of stroke

h/o medication use

h/o viral hepatitis , jaundice, liver disease

h/o bariatric surgery

h/o TPN

h/o alcohol consumption /drinking pattern

EXAMINATION

HEIGHT:

WEIGHT:

BMI:

BLOOD PRESSURE: **PULSE RATE:**

RECORDINGS	1ST READING	2ND READING
SITTING		
SUPINE		
STANDING		

GENERAL EXAMINATION

CVS:

RS:

P/A:

CNS:

1. **TENDON REFLEX**
2. **VIBRATION SENSATIONS**
3. **FUNDUS EXAMINATION**

INVESTIGATION

1. Blood glucose –fasting postprandial

2. Lipid profile

3. Liver function test with enzymes

4. Ultrasonogram

5. Urine spot albumin creatinine ratio

6. ECG

7. Carotid Doppler –Carotid Intimal Thickness

8. Ankle Brachial Index (oscillometric method)

Signature of Investigator **Signature of Guide**

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NAME	age	sex	DURATION OF DIABETES	SBP	DBP	HEIGHT	WEIGHT	BMI	FASTING	POSTPRANDIAL	UREA	CREATININE	ACR	TGL	totcho	ABI	NAFLD	RETINO	IHD	PERINER	CVA	CIMT	AST	ALT	TOTAL PROTEIN	ALBUMIN	GFR LESS THAN 30

RAVI	65	M	10	140	84	166	74	26.85	140	190	35	1.1	60	150	210	0.8	YES	YES	NO	YES	YES	1.1	106	141	7.2	4	NO
RAMESH	66	M	5	130	82	145	60	28.53	130	170	33	0.9	10	135	245	1	YES	YES	YES	YES	NO	1	35	24	6.9	3.9	NO
KUMAR	45	M	7	120	82	155	55	22.89	170	199	28	0.7	100	180	210	0.98	NO	NO	YES	NO	NO	0.6	41	42	7	3.8	NO
SENTHIL	48	M	6	150	80	147	57	26.37	110	180	24	0.6	50	140	198	0.7	YES	YES	NO	YES	NO	0.5	34	33	7.1	4	NO
SARAVANAN	58	M	7	124	110	182	82	24.75	90	150	24	0.8	10	145	187	0.7	YES	NO	YES	NO	NO	0.6	31	35	6.9	4.1	NO
SATHISH	65	M	5	150	84	166	74	26.80	80	154	29	0.9	10	165	245	1	NO	NO	NO	NO	NO	0.7	33	41	7.5	4	NO
VASANTH	38	M	2	124	94	164	75	27.88	86	185	28	0.7	10	125	265	0.98	YES	NO	YES	NO	YES	0.9	24	27	7.5	4.2	NO
UMA	56	F	4	130	110	166	70	25.40	88	160	27	0.8	50	135	274	0.99	NO	NO	YES	NO	NO	0.8	40	41	7.1	4.4	NO
GEETHA	45	F	3	140	90	150	55	24.44	99	188	29	0.9	10	125	265	1.1	YES	YES	YES	NO	YES	0.6	40	45	7.4	4.2	NO
PANDIAN	48	M	4	124	110	174	96	31.70	100	210	24	0.7	20	245	235	0.6	NO	NO	NO	NO	NO	0.67	34	35	6.9	4	NO
LAKSHMI	66	F	5	150	84	160	50	19.53	117	200	25	0.8	10	124	245	0.7	NO	YES	NO	YES	NO	0.99	31	35	6.8	4.1	NO
ARUNA	58	F	4	124	94	149	56	25.22	147	190	36	1.4	40	102	241	0.99	YES	NO	NO	NO	NO	1.1	31	35	7	4.1	NO
NAVANEETHAM	51	F	3	140	94	166	74	26.85	165	210	34	1.6	400	132	201	0.94	YES	NO	NO	NO	NO	0.6	33	32	7.6	4.1	NO
VELAN	42	M	4	130	82	170	70	24.22	185	220	29	1	10	132	206	0.96	YES	NO	YES	NO	NO	0.7	37	34	7	3.8	NO
RAJALA	51	F	5	120	83	166	74	26.	145	180	25	0.7	10	158	245	1	NO	NO	NO	NO	NO	0.6	38	35	7	4	NO

KSHMI								85																			
SAROJA	55	F	7	110	80	149	48	21.62	128	145	86	2.4	400	165	280	0.97	NO	YES	NO	NO	YES	0.6	34	45	5.6	3	YES
GOWRI	64	F	3	124	74	149	56	25.22	157	165	24	0.7	10	184	275	0.3	YES	NO	NO	NO	NO	0.8	41	42	6.9	3.9	NO
VIDHYA	58	F	4	140	84	142	54	26.78	165	190	26	0.9	10	165	215	0.9	YES	NO	YES	YES	NO	0.6	41	43	7.5	4	NO
DEVI	55	F	3	130	82	166	70	25.40	185	210	34	0.8	10	198	246	0.2	NO	NO	YES	NO	NO	0.4	43	42	7.5	4.6	NO
JENIFER	65	F	4	120	82	165	68	24.97	135	165	35	0.7	10	132	275	1.1	YES	YES	YES	NO	NO	0.6	41	42	7.4	4.7	NO
SANDYA	45	F	3	110	80	152	52	22.50	147	180	36	0.8	10	145	235	1.1	NO	NO	NO	NO	NO	0.7	40	42	7	4	NO
KARTHIK	54	M	4	124	74	172	70	23.66	198	240	37	1.1	10	245	247	0.9	NO	NO	Y	NO	NO	0.6	47	35	7	4.1	NO
SHAIK	58	M	5	150	84	155	65	27.05	185	236	26	0.7	30	175	261	0.8	NO	NO	Y	YES	NO	0.8	32	36	6.5	4	NO
BASHEER	47	M	1	124	94	183	69	20.60	110	140	28	0.8	40	245	217	0.7	NO	YES	Y	NO	NO	0.9	37	33	6.5	3.4	NO
RESHMA	69	F	7	120	94	152	65	28.13	100	130	29	0.7	10	198	247	1	YES	NO	NO	NO	NO	0.7	32	39	7	4.4	NO
SALMA	48	F	6	110	100	148	48	21.91	171	190	24	0.7	20	145	216	0.99	NO	NO	Y	NO	YES	0.5	37	36	7.1	4.3	NO
SARASWATHY	58	F	3	110	100	156	52	21.36	140	165	34	1	60	132	247	0.98	NO	NO	NO	NO	NO	0.7	30	37	7.1	4.1	NO
VENKAT	65	M	2	140	80	174	78	25.76	110	140	35	1	40	154	217	1	YES	NO	NO	NO	NO	0.8	38	33	6.2	3	NO
RAMYA	38	F	1	120	100	145	56	26.63	90	120	47	1.8	10	145	265	1.1	YES	YES	Y	NO	NO	0.7	38	37	7.5	4.4	NO
RE	6	F	8	1	8	1	6	2	8	11	4	1.	1	1	2	0	Y	N	N	Y	N	0	3	3	6	3.	NO

VATHI	60			10	0	54	5	7.40	0	4	9	7	0	65	45	.8	ES	O	O	ES	O	.9	7	2		1	
HARI	55	M	4	124	74	177	87	27.76	90	124	42	1	10	175	246	0.7	YES	YES	Y	NO	NO	0.6	36	34	6.6	3.3	NO
SETU	47	M	2	150	84	181	60	18.31	88	132	41	0.7	40	168	275	0.6	YES	NO	NO	NO	NO	0.7	37	37	7	4	NO
SARANYA	58	F	3	124	94	165	69	25.34	75	142	34	0.8	10	135	265	0.8	YES	NO	NO	NO	NO	0.8	33	38	7	4.2	NO
RUKMANI	65	F	4	110	94	170	80	27.68	112	132	35	0.8	10	135	264	0.99	NO	NO	NO	NO	NO	0.9	25	37	6.9	4.1	NO
RAJAMANI	64	F	3	170	86	169	68	23.80	121	145	36	0.8	10	245	245	1	NO	NO	NO	NO	NO	0.7	30	34	6.8	4	NO
SETHA	69	F	5	140	120	162	58	22.10	132	157	34	0.8	10	127	265	1.1	NO	YES	Y	NO	YES	0.8	24	23	6.8	3.9	NO
MUNNIAMMA	68	F	5	150	100	154	64	26.98	142	165	31	0.7	10	145	265	1.2	YES	NO	NO	YES	NO	0.9	30	37	6.9	3.8	NO
SIVA	67	M	4	140	70	154	57	24.03	110	140	32	0.9	30	145	265	0.8	NO	NO	NO	NO	NO	0.7	37	32	7.1	4.1	NO
SANTHOSHAMMAL	63	F	7	160	90	184	102	30.12	90	120	36	0.7	20	245	245	0.56	NO	NO	NO	NO	NO	0.8	31	36	6.9	4.2	NO
DINESH	61	M	3	150	100	175	87	28.40	96	110	33	0.8	20	85	235	1.2	YES	NO	Y	NO	NO	0.7	39	34	7.5	4.4	NO
ARUNA	67	M	5	160	90	181	84	25.64	98	142	32	0.9	40	245	275	1	NO	NO	NO	NO	NO	0.6	27	36	7.5	4.7	NO
JEYA	54	F	4	140	90	152	52	22.50	110	115	30	0.8	50	245	247	1.2	YES	YES	NO	NO	NO	0.6	42	37	6.4	3.2	NO
SHAKTHI	51	F	6	150	80	147	57	26.37	85	124	30	0.7	40	174	265	0.8	YES	NO	Y	NO	NO	0.7	32	39	7	4	NO
RAJ	53	M	3	150	80	174	84	27.	75	116	31	0.8	40	147	275	0.4	YES	NO	Y	YES	NO	1.1	117	175	6.9	4.2	NO

								74																		
VIJAYA	51	F	7	170	70	156	64	26.29	95	147	32	0.8	10	144	298	0.7	NO	NO	NO	NO	NO	0.6	38	35	7.5	4.1	NO
RAMAN	57	M	7	150	78	174	74	24.44	65	114	36	0.9	20	165	215	0.4	YES	NO	NO	NO	YES	0.6	34	45	7.4	4.2	NO
RAJENDERAN	58	M	5	140	80	177	87	27.76	140	156	25	0.8	30	135	214	1	NO	NO	NO	NO	NO	0.8	41	42	7.1	4	NO
SATHYA	56	F	6	110	80	146	64	30.02	95	147	46	1.7	10	165	216	1.1	NO	NO	NO	NO	NO	0.6	41	43	6.9	4.7	NO
REKHA	47	F	5	150	80	177	87	27.76	85	154	47	1.2	10	175	265	0.8	YES	YES	NO	NO	NO	0.4	43	42	7.5	4.1	NO
DARWIN	57	M	2	140	86	166	68	24.67	76	157	41	0.8	40	245	204	1.1	NO	NO	NO	NO	NO	0.6	41	42	7.5	4.2	NO
GOWRIBAI	58	F	3	140	80	147	57	26.37	141	165	57	1.8	4	245	265	1.3	YES	NO	NO	YES	NO	1	40	42	6.2	3	NO
RAMAN	56	M	2	110	110	184	84	24.81	85	124	58	1.7	22	174	214	1	NO	NO	NO	NO	NO	0.8	47	35	6	2.8	NO
SYEDIQBAL	51	M	7	110	80	175	75	24.49	96	135	42	1.1	20	245	214	1	NO	NO	NO	NO	NO	0.6	41	42	7.1	4.3	NO
RAJESWARI	65	F	4	140	86	164	62	23.05	110	147	24	0.8	20	175	265	1	YES	NO	Y	NO	YES	0.7	40	42	7	4	NO
KURUSHABEGUM	53	F	4	130	82	149	58	26.12	140	168	26	0.9	20	245	247	1	NO	YES	NO	NO	NO	0.6	47	35	7.1	4.2	NO
UMANANDHA	54	M	4	170	82	174	69	22.79	171	198	22	0.7	30	165	206	1	YES	YES	NO	YES	YES	0.6	145	210	6.9	4.1	NO
SWARNA	54	F	7	110	80	151	56	24.56	140	185	28	0.9	40	175	208	1	NO	NO	NO	NO	NO	0.7	24	23	7.5	4.1	NO
SANKAR	58	M	9	124	74	169	82	28.71	85	168	29	0.8	20	158	207	1	YES	NO	NO	NO	NO	0.7	30	37	7.5	4	NO

VIJI	59	F	11	100	84	181	81	24.72	90	130	31	0.5	30	165	204	1.1	YES	NO	NO	NO	NO	0.6	37	32	6.7	4.2	NO
MANICKAM	57	M	3	110	60	182	95	28.68	80	140	32	0.8	40	124	206	0.8	NO	NO	NO	NO	NO	0.6	31	36	7	4.2	NO
MALATHY	47	F	2	134	84	165	59	21.67	90	126	31	0.8	30	175	207	0.9	NO	NO	NO	YES	NO	0.8	39	34	6.7	4.3	NO
VIJYA	48	F	1	110	64	171	65	22.23	88	142	36	0.8	40	185	208	0.7	NO	NO	NO	NO	NO	0.7	27	36	6.4	3.2	NO
VANI	45	F	2	114	90	164	58	21.56	96	156	35	0.7	10	135	207	0.6	NO	NO	Y	NO	NO	0.6	37	34	7	4	NO
AMSA	41	F	3	150	84	159	69	27.29	99	142	34	0.9	30	185	165	0.8	NO	NO	NO	NO	NO	0.8	38	35	7.5	4.2	NO
VARALAKSHMI	42	F	1	160	90	172	56	18.93	140	185	38	0.8	20	175	165	0.99	NO	YES	Y	NO	NO	0.7	34	45	6.9	4.3	NO
SNEKA	45	F	5	140	90	148	48	21.91	130	175	37	0.8	10	165	214	1	NO	NO	NO	NO	YES	0.6	41	42	7.5	4.7	NO
SATHYAVATHY	57	F	3	170	64	156	64	26.29	170	210	34	0.8	10	185	214	1.1	NO	NO	NO	NO	NO	0.97	41	43	7.5	4.3	NO
MUMTAJ	56	F	4	134	65	148	52	23.74	110	140	42	0.8	10	175	214	1.2	NO	NO	NO	NO	NO	0.7	42	42	7.6	4.7	NO
RAHAMATH	58	F	2	110	64	153	57	24.35	90	110	46	0.7	40	185	247	1.1	NO	NO	NO	NO	NO	0.7	41	42	7	4.6	NO
SELVI	52	F	4	114	90	169	75	26.25	80	165	48	0.6	40	102	245	0.8	NO	NO	NO	NO	NO	0.6	40	42	7	4	NO
KAMALA	54	F	2	150	84	147	57	26.37	86	147	88	0.8	1	165	278	0.7	YES	NO	NO	NO	NO	0.6	47	35	6.8	3.8	NO
BASHEER	51	M	1	160	90	148	69	31.50	88	134	65	0.7	20	145	241	1.1	YES	YES	Y	YES	NO	0.6	24	23	7	3.6	NO
BABU	59	M	6	14	90	17	69	22	12	154	47	0.5	1	13	21	1.	NO	NO	NO	NO	NO	0.	30	37	6.3	3.4	NO

				0		7		.02	8					5	6	1						6					
SETHAMMA	56	F	4	134	64	153	62	26.48	157	169	41	1.1	50	168	275	1	NO	NO	NO	NO	NO	0.6	37	32	6.8	3.7	NO
PACHIYAMMA	54	F	3	110	64	162	72	27.43	165	198	24	1.2	60	198	214	1	NO	NO	NO	NO	NO	0.6	31	36	6.4	3	NO
NOORJAGAN	54	F	2	114	90	163	61	22.96	185	256	95	1.7	20	199	216	1.2	NO	NO	NO	NO	NO	0.6	39	34	6.2	3	NO
DHANAM	57	F	2	150	84	172	62	20.95	135	217	25	1.2	10	135	275	1.1	NO	YES	NO	YES	NO	0.8	27	36	7	3.4	NO
MUTHAMMAL	59	F	1	160	90	164	62	23.05	147	220	34	1	20	178	241	0.8	NO	NO	NO	NO	NO	0.8	38	35	7.5	4	NO
AMUTHA	58	F	4	110	90	163	74	27.85	198	245	35	1	30	187	214	0.4	NO	NO	Y	NO	NO	0.7	34	45	7.4	4.5	NO
SUMATHI	56	M	3	140	86	179	84	26.21	98	147	33	0.8	40	198	214	0.85	YES	NO	NO	NO	NO	0.8	41	42	7.1	4	NO
KALYANI	51	F	2	140	90	154	54	22.77	114	194	31	0.8	10	187	235	0.6	NO	NO	NO	NO	NO	0.8	41	43	7.3	4	NO
JEGAN	52	M	7	130	82	155	65	27.05	165	241	32	0.8	40	178	221	0.75	YES	YES	NO	NO	NO	0.8	43	42	7.5	4	NO
GANAPATHY	54	M	2	120	100	187	78	22.30	145	211	30	0.7	20	165	212	0.94	NO	NO	NO	NO	NO	0.7	41	42	7.6	4.7	NO
RANGANATHAN	65	M	3	150	80	175	69	22.53	140	196	25	0.8	20	145	201	0.97	YES	YES	NO	YES	NO	0.8	40	42	7.2	4	NO
SHAKEERABANU	58	F	2	124	100	169	64	22.40	85	124	22	1	10	165	192	0.92	NO	NO	NO	NO	NO	0.6	47	35	7.6	4.6	NO
DAYALAN	57	M	4	140	84	174	75	24.77	75	165	22	1	10	125	165	0.97	NO	NO	Y	NO	NO	0.78	43	42	7.1	4	NO
PALAYAM	59	F	1	170	90	171	65	22.2	95	149	29	0.8	40	148	165	0.98	NO	NO	NO	NO	NO	0.87	41	42	6.9	4	NO

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MOHANBABU	54	M	3	150	76	181	74	22.58	65	182	28	0.8	40	169	185	0.97	YES	YES	NO	YES	YES	0.9	40	42	7.5	4.2	NO
SUNDARAJAN	56	M	2	140	100	174	69	22.79	140	198	24	0.8	10	125	165	0.94	NO	NO	NO	NO	NO	0.7	47	35	7.5	4.3	NO
GOVINDHARAJU	51	M	7	130	82	172	69	23.32	95	174	34	0.8	10	135	165	0.91	NO	YES	NO	NO	NO	0.5	24	23	7.3	4.2	NO
SHAKUNTHALA	52	F	2	170	82	164	58	21.56	85	164	31	0.9	10	175	265	1	YES	NO	Y	NO	NO	0.97	38	35	7.5	4.3	NO
MONISHA	56	F	6	160	84	164	71	26.39	140	184	39	0.9	70	195	214	1	YES	NO	NO	YES	NO	1.2	34	45	7	4.1	NO
KANNIAMMA	54	F	7	124	74	164	54	20.07	171	198	33	1	44	175	247	1.1	NO	NO	NO	NO	NO	1.4	41	42	7	4	NO
SHEIKMUBARAK	57	M	2	110	84	181	69	21.06	140	175	88	1.3	200	185	246	1.2	NO	NO	NO	NO	NO	0.6	41	43	6.2	3	NO
UTHRINATAHAN	58	M	5	114	90	183	75	22.39	110	198	41	1	10	154	285	1	NO	NO	Y	NO	NO	1.2	43	42	7	4.1	NO
RANGANATHAN	59	M	6	150	84	174	65	21.47	90	147	24	0.8	200	156	235	1	NO	YES	NO	NO	YES	1.1	41	42	7.1	4	NO
SHAMEEN	52	F	4	110	90	171	65	22.23	80	167	29	0.8	10	159	154	1	NO	NO	NO	NO	NO	0.6	40	42	6.9	3.9	NO
PUNITHAM	54	F	2	134	80	167	58	20.79	90	128	32	0.7	10	184	175	0.7	NO	NO	Y	NO	NO	0.7	47	35	7.5	3	NO
KUPPU	57	F	4	150	64	156	64	26.29	88	187	33	0.8	100	194	145	0.8	YES	NO	Y	YES	NO	0.7	45	47	6	2.8	NO
KRISHNAN	56	M	4	114	90	175	69	22.53	84	154	74	3.2	300	194	165	1	NO	YES	NO	NO	NO	0.8	42	43	6	3	YES

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.1223/ME-1/Ethics/2013 Dt:07.03.2013.
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on Non alcoholic fatty liver disease in type 2 Diabetes mellitus An independent predictor for Macroangiopathy and Microangiopathy" for research work submitted by Dr.K.Mohanraj, MD (GM), PG Student, Govt. Kilpauk Medical College, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the course of the study any change in the protocol and patient information informed consent and asks to be provided a copy of the final report.

CHAIRMAN, 19/4
Ethical Committee
Govt.Kilpauk Medical College,Chenn

GOVT. KILPAUK MEDICAL COLLEGE
19 APR 2013
Kilpauk, Chennai-10.

நோயாளி ஒப்புதல் படிவம்

ஆராய்ச்சியின் விவரம்:

ஆராய்ச்சி மையம்: அரசு கீழ்பாக்கம் மருத்துவக் கல்லூரி மருத்துவமனை

நோயாளியின் பெயர்: நோயாளியின் வயது:

பதிவு எண்:

1. மேற்குறிப்பிட்டுள்ள ஆராய்ச்சியின் நோக்கத்தையும் பயனையும் முழுவதுமாக புரிந்துகொண்டேன். மேலும் எனது அனைத்து சந்தேகங்களையும் கேட்டு அதற்கான விளக்கங்களையும் தெளிவுபடுத்திக் கொண்டேன்.
2. மேலும் இந்த ஆராய்ச்சிக்கு எனது சொந்த விருப்பத்தின் பேரில் பங்கேற்கிறேன் என்றும், மேலும் எந்த நேரத்திலும் எவ்வித முன்னறிவிப்புமின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழுமையான உரிமை உள்ளதையும், இதற்கு எவ்வித சட்ட பிணைப்பும் இல்லை என்பதையும் அறிவேன்.
3. ஆராய்ச்சியாளரோ, ஆராய்ச்சி உதவியாளரோ, ஆராய்ச்சி உபயத்தாரோ, ஆராய்ச்சி பேராசிரியரோ, ஒழுங்குநெறி செயற்குழு உறுப்பினர்களோ எப்போது வேண்டுமானாலும் எனது அனுமதியின்றி எனது உள்நோயாளி பதிவுகளை இந்த ஆராய்ச்சிக்காகவோ அல்லது எதிர்கால பிற ஆராய்ச்சிகளுக்காகவோ பயன்படுத்திக்கொள்ளலாம் என்றும் மேலும் இந்த நிபந்தனை நான் இவ்வராய்ச்சியிலிருந்து விலகினாலும் தகும் என்றும் ஒப்புக்கொள்கிறேன். ஆயினும் எனது அடையாளம் சம்பந்தப்பட்ட எந்த பதிவுகளும் (சட்டபூர்வமான தேவைகள் தவிர) வெளியிடப்படமாட்டது என்ற உறுதிமொழியின் பெயரில் இந்த ஆராய்ச்சியிலிருந்து கிடைக்கப்பெறும் முடிவுகளை வெளியிட மறுப்பு தெறிவிக்கமாட்டேன் என்று உறுதியளிக்கின்றேன்.

4. இந்த ஆராய்ச்சிக்கு நான் முழுமனதுடன் சம்மதிக்கின்றேன் என்றும் மேலும் ஆராய்ச்சிக் குழுவினர் எனக்கு அளிக்கும் அறிவுரைகளை தவறாது பின்பற்றுவேன் என்றும் உறுதியளிக்கின்றேன்.
5. இந்த ஆராய்ச்சிக்குத் தேவைப்படும் அனைத்து மருத்துவப் பரிசோதனைகளுக்கும் ஒத்துழைப்பு தருவேன் என்று உறுதியளிக்கின்றேன்.
6. இந்த ஆராய்ச்சிக்கு யாருடைய வற்புறுத்தலுமின்றி எனது சொந்த விருப்பத்தின் பேரிலும் சுயஅறிவுடனும் முழுமனதுடனும் சம்மத்திக்கின்றேன் என்று இதன் □ லம் ஒப்புக்கொள்கிறேன்.

நோயாளியின் கையொப்பம் / பெருவிரல் கைரேகை

இடம்: தேதி:

ஆராய்ச்சியாளரின் கையொப்பம்

இடம்: தேதி: