PREVALENCE OF NON ALCOHOLIC FATTY LIVER DISEASE IN DIABETICS

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BONAFIDE CERTIFICATE

*This is to certify that this dissertation entitled "***PREVALENCE OF NON ALCOHOLIC FATTY LIVER DISEASE IN PATIENTS WITH DIABETES***" is the bonafide work done by* **Dr.AARTHI SURENDRAN**, *under my direct guidance and supervision in the Department of Internal Medicine, Kilpauk Medical College, Chennai-10, in fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University for the award of M.D. degree branch I, Part II (General Medicine) during this period of study from May 2004 - March 2007.*

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CONTENTS

SERIAL NO.	TITLE	PAGE NO
1.	Introduction	1
2.	Aim of the Study	2
3.	Review of Literature	3
4.	Materials and Methods	43
6.	Results	46
7.	Discussion	50
8.	Conclusion	53
9.	Bibliography	54
10.	Proforma	61
11.	Master Chart	63

INTRODUCTION

The incidence of diabetes in India is 3.8%[34]. It is well known that diabetes is a systemic disease, it affects almost all organ systems.Non-alcoholic fatty liver disease (NAFLD) is being increasingly recognized today as a potentially serious complication of diabetes, especially type 2. The spectrum of NAFLD extends from simple steatosis or steatosis with mild inflammation to severe non-alcoholic steatohepatitis (NASH). The pathophysiology and treatment remain unclear in many respects, but much progress has been made since the introduction of the terms non-alcoholic steatohepatitis (NASH) in 1980 and non-alcoholic fatty liver disease (NAFLD) in 1986. [1, 2]

AIM

The aim was to analyse the prevalence of fatty liver (non alcoholic fatty liver disease) in patients with diabetes.

REVIEW OF LITERATURE

THE ROLE OF LIVER IN GLUCOSE HOMEOSTASIS:

The concentration of blood glucose is regulated within narrow limits. In the post absorptive state the concentration of blood glucose in individual humans and many mammals is set within the range of 4.5 – 5 mmol/L. After ingestion of a carbohydrate meal it may rise to 6.5 – 7.2 mmol/L. During fasting the levels fall to 3.3 – 3.9 mmol/L.[3]

Blood glucose is derived from the diet, gluconeogenesis and glycogenolysis. Dietary carbohydrates that are actively digested contain glucose, galactose and fructose residues. These are transported to the liver via the portal vein. Galactose and fructose are readily converted to glucose by the liver. Glucose is formed from glucogenic compounds, which fall in two categories:

1. those that involve direct net conversion to glucose without significant recycling such as amino acids and propionate.
2. those which are products of partial metabolism of glucose in certain tissues and are converged to the liver and kidney to be resynthesised to glucose, Eg: lactic acid and glycerol

During starvation amino acids are transported from muscles (especially alanine)[3] to liver for gluconeogenesis. The energy required for the hepatic synthesis of glucose from pyruvate is derived from oxidation of fatty acids.

Liver cells are fully permeable to glucose (via the GLUT 2 receptors) where as the cells of extra hepatic tissues except the pancreatic islets are relatively impermeable [3], therefore the passage through the cell membrane is the rate limiting step in the uptake of glucose in extra hepatic tissues. The concentration of glucose in the blood is an important factor that controls the rate of uptake in liver and extra hepatic tissues. It is probable that the activity of certain enzymes and concentration of key intermediates exert a direct effect on the uptake of glucose by the liver.[3]

The enzyme glucokinase is important in regulating blood glucose after a meal. The enzymes hexokinase found in extra hepatic tissues is inhibited by glucose-6-phosphate, therefore some feedback control may be exerted on glucose uptake in extra hepatic tissues. The liver is not subject to this constraint because glucokinase is not affected by glucose-6-phosphate.[3]

At normal systemic blood glucose concentrations (4.5 – 5.5 mmol/L), the liver appears to be the net producer of glucose. However, as the glucose level rises the output of glucose ceases, so that at high levels there is net uptake of glucose. [3]

Insulin plays a central role in regulating blood glucose. It is produced by the B-cells of the islets of Langerhans in the pancreas as a direct response to the degree of hyperglycemia. The islet cell is freely permeable to glucose via the GLUT 2 receptors. Therefore, the blood glucose concentration determines the flux through glycolysis, the citric acid cycle and generation of ATP. Increased ATP concentration inhibits the ATP sensitive potassium channels causing depolarization of the B-cell membrane, which increases the calcium influx via voltage sensitive calcium channels stimulating exocytosis of insulin.[4]

Other substances causing release of insulin from the pancreas include amino acids, free fatty acids, ketone bodies, glucagons, and secretin and

sulfonylurea drugs. Insulin increases glucose uptake in adipose tissue and muscle.

There is no direct effect of insulin on glucose penetration of hepatic cells, however insulin does indirectly enhance long-term uptake of glucose by liver as a result of its actions on the synthesis of enzymes controlling glycolysis, glycogenesis and gluconeogenesis.

Glucagon opposes the actions of insulin. It causes glycogenolysis by activating phosphorylase in the liver and it enhances gluconeogenesis from amino acids and lactate. Most of the endogenous glucagons and insulin are cleared from the circulation by the liver. Unlike adrenalin, glucagon does not have an effect of muscle phosphorylase.

Other hormones that increase blood glucose include:

- ACTH
- Growth Hormone – by decreasing glucose uptake in certain tissues and by mobilizing free fatty acids from adipose tissue which themselves inhibit glucose utilization.
- Glucocorticoids -by increasing gluconeogenesis and by inhibiting utilization of glucose in extra hepatic tissues.
- Epinephrine –by causing glycogenolysis in liver and muscle.
- Thyroid hormone.

The liver, kidney, intestine and platelets contain the enzyme glucose-6-phosphatase which produces glucose from glucose-6-phosphate and is the final step in the production of glucose via gluconeogenesis. This enzyme is absent in other tissues. Glucose that is metabolized peripherally may therefore be converted back to glucose or hepatic glycogen via gluconeogenesis with lactate as primary substrate, this is known as Cori's cycle.

In type 2 diabetes, excessive hepatic glucose output constitutes to the fasting hyperglycemia. Increased gluconeogenesis is the predominant mechanism responsible for this increased output, while glycogenolysis has not been shown to be increased in patients with type 2 diabetes.[5]

LIVER DISEASE OCCURING AS A CONSEQUENCE OF DIABETES MELLITUS:

GLYCOGEN DEPOSITION:

Excess glycogen accumulation in the liver is seen in 80% of diabetic patients.[6] Glycogen synthesis in the liver is impaired in diabetes due to defective activation in glycogen synthase. In patients with chronic diabetes, glycogen accumulation is seen and is postulated that long standing insulin deficiency may actually facilitate synthase activity. This and enhanced gluconeogenesis may account for the net accumulation of glycogen in diabetes.

The mechanisms of cytoplasmic glycogen deposition is uncertain but is perhaps related to the large variations in glucose concentration and frequent insulin dosing. Now correlation between hepatic glycogen content and fasting blood glucose levels has been demonstrated.[7] It is postulated that glycogen is actually synthesized in the nucleus and has been found in 60 – 75% of diabetic patients.[8, 9]

The finding of glycogen nuclei in a patient with fatty liver is useful confirmatory evidence that fatty liver is secondary to diabetes even if the glucose tolerance test is normal.

Patients showing solely excessive glycogen deposition may exhibit hepatomegaly and liver enzyme abnormalities and may have abdominal pain and vomiting and rarely ascites. All these abnormalities may improve with sustained glucose control.[10]

NON-ALCOHOLIC FATTY LIVER DISEASE:

HISTORICAL PERSPECTIVE:

Various types of fatty infilteration of the liver were classified by Virchow in the 1800s[11]. During this time the color shape and the firmness of fatty liver were described by pathologists and fat globules were proved to lie within the hepatic cells rather than the interstitium.[12]

Zelman reported the existence of liver damage with fibrosis and early cirrhosis in obese patients without a significant history of alcohol consumption. This account resurfaced more recently in the case of patients who had undergone bypass surgery for morbid obesity. [13 – 18]

The association was widely attributed at that time to protein calorie malnutrition or intestinal bacterial overgrowth, although a correlation between obesity and diabetes and possible liver damage was not strongly emphasized.

DEFINITIONS AND TERMS:

Non alcoholic fatty liver disease (NAFLD):

Sometimes referred to as non alcoholic fatty liver. Indicates the presence of fatty infilteration of the liver defined as exceeding 5% weight and frequently taken as fat in >5% of hepatocytes. Includes non alcoholic steatohepatitis.

Simple steatosis:

A type of fatty infilteration (NAFLD) with no or minimal inflammation and no fibrosis.

Non alcoholic steatohepatitis (NASH):

A type of NAFLD with inflammation and fibrosis, usually beginning around the central vein and may progress to cirrhosis.

Primary NASH:

This term is occasionally encountered in literature but not widely accepted. It indicates typical NASH associated with central obesity and often type 2 DM, but without a specific, additional etiologic factor. The likelihood that many cases of secondary NASH represent unrecognized or exacerbated 'primary' NASH makes the term less useful.

Secondary NASH:

NASH associated with a specific problem such as the effect of a drug or bariatric surgery. Many patients may have exacerbation of underlying NASH, making the distinction less useful.

"Presumed" NASH or NAFLD:

In several epidemiologic and pediatric studies, NASH has been used as presumptive diagnosis because of abnormal liver enzyme levels, negative

results of viral studies and echogenic or 'bright' liver at ultrasonography consistent with fatty infilteration.

EPIDEMIOLOGY OF FATTY LIVER:

NASH is one of the most common of all liver diseases. Obesity, type 2 diabetes and hyperlipidemia have been the most constant conditions associated with steatosis and steatohepatitis and are predictors of more severe histologic disease.[19] Diabetes was also identified as an independent risk factor for NASH.[20] Hypertriglyceridemia is also identified as an independent predictor of steatosis at liver ultrasound imaging.

Insulin resistance is common in NASH patients and hyperinsulinemia may play a pathogenic role in the progression of NASH, even in the absence of overt diabetes.[21,22] It is estimated that as many as 75% of patients with type 2 DM have fatty infilteration. Fatty infilteration also has been found to precede the development of overt diabetes. The progression to more overt diabetes in these patients may depend on additional factors such as peripheral fat metabolism, pancreatic islet cell vitality and the stage of liver

fibrosis. The severity of liver injury worsens with the degree of abnormal glucose metabolism in obese patients.[24]

As mentioned earlier, hypertriglyceridemia been identified as a predictor both of steatosis at ultrasound examination and of more extensive fibrosis at biopsy in patients with NASH[25]. It is estimated that two thirds of patients with hypertriglyceridemia and one third of those with hypercholesterolemia have fatty liver.[26]

NAFLD and NASH have been described in patients without the classic risk factors of obesity, diabetes and overt hyperlipidemia. This group appears to contain relatively younger men with milder histologic changes and with visceral or central adiposity and hyperinsulinemia.

CONDITIONS ASSOCIATED WITH NON-ALCOLHOLIC FATTY LIVER:

Metabolic factors:

- Obesity (truncal or central obesity)
- Type 2 diabetes
- Hyperlipidemia

Specific conditions associated with fatty infilteration of liver:

- Metabolic syndrome X
- Lipodystrophy
- Mitochondrial diseases
- Weber Christian Disease

Bariatric surgery:

- Jejuno ileal bypass
- Gastric bypass or gastroplasty

Medications:

- Methotrexate
- Amiodarone
- Tamoxifen
- Nucleoside analogues

Parentral nutrition and malnutrition:

- Total parentral nutrition
- Kwashiokar
- Celiac disease

Miscellaneous:

- Wilson’s disease
- Toxins (carbon tetrachloride, per chloroethylene, phosphorous, ethyl bromide)

CLINICAL CRITERIA:

By definition, the criteria for NASH requires exclusion of alcohol as an etiologic agent. Results of recent studies indicate that steatosis (possibly mediated by core protein metabolism) accelerates liver disease in patients with chronic hepatitis C.

HISTOLOGIC CRITERIA:

Steatosis, is defined as hepatic fat exceeding 5% total body weight and usually taken as fat identifiable in more than 5% of hepatocytes, is an essential feature of NAFLD.

Within the spectrum of NAFLD, the term NASH indicates a more severe type of limb injury and worse prognosis than simple steatosis, which is differentiated by absence of inflammation or fibrosis and appears to have a long term stable course.

In the original description of NASH, Ludwig et al described the presence of diffuse or pericentral vein (perivenular) macrovesicular fat along with a mixed inflammatory infileterate (neutrophils and lymphocytes) in the perivenular area and associated with focal necrosis.[1]Other findings in NAFLD include glycogenated nuclei[35,36] portal inflammation, microvesicular fat droplets and lipogranuloma.[37,38]

Accurate evaluation of fatty liver sample requires use of collagen stain (Masson trichrome) as well as eosin and hematoxylin.

CLASSIFICATION AND STAGES OF NAFLD AND NASH:

CLASSES OF NAFLD:[39]

Class I – Simple steatosis (no inflammation or absent fibrosis)

Class II – Steatosis with lobular inflammation but absent fibrosis or balloon cells

Class III – Steatosis plus inflammation and fibrosis of varying degrees

Class IV – Steatosis, inflammation, fibrosis, balloon cells and Mallory Hyaline bodies

FIBROSIS STAGES OF NASH: [40]

Stage I – Zone 3, pericentral vein, sinusoidal or pericellular fibrosis

Stage II – Zone 3 sinusoidal fibrosis and zone 1 periportal fibrosis

Stage III – Bridging between zone 3 and zone 1

Stage IV – regenerating nodules indicating cirrhosis

CRYPTOGENIC CIRRHOSIS:

Serial biopsy studies have established the progression of NASH to a stage of bland cirrhosis. The loss of fatty infilteration may be the result of altered blood flow or decreased sinusoidal permeability and lipoprotein delivery as the liver becomes fibrotic. Some nodules occasionally show focal fatty changes.

FOCAL STEATOSIS AND FOCAL SPARING:

In as series of patients with various forms of fatty liver disease detected radiographically, focal steatosis was evident in 15% and focal sparing (usually of the caudate lobe) seen in 9%.[41] Variations in blood flow with resulting differences in insulin exposure and nutrient delivery is thought

to explain both focal sparing and focal steatosis.[42,43] Histologic features of these lesions vary from simple steatosis to steatohepatitis.

SYMPTOMS AND SIGNS:

Most of the patients are asymptomatic. Fatigue is seen is approximately 70% of the patients and right upper quadrant pain is seen in 50% of the patients.

Hepatomegaly is usually caused by steatosis but can be caused by hepatic glycogenosis in diabetic patients.[27]

Acanthosis nigricans is seen in some children with NASH.[28]
The presence of palmar erythema or spider angiomas suggests the presence of cirrhosis.

A family history of fatty liver, unexplained liver abnormalities or cryptogenic cirrhosis is present in approximately 20 – 25% of the cases.[29]

LABORATORY FINDINGS:

Many patients have only abnormal liver function test as the initial manifestation of NASH. The aspartate transaminase and amino transaminase levels are elevated usually less than two times the upper limit of normal.[12]The level of AST, which is usually mitochondrial in origin is, correlates well with the extent of histologic injury. The AST/ALT ratio also correlates with the extent of histologic injury, wherein ratio of greater than 1 often indicate the presence of fibrosis and ratio of less than 1 are consistent with mild disease. Gamma glutamyl transferase is also elevated and is usually less than 400IU/L.
Patients with marked histologic changes may have normal enzyme levels. The use of certain anti diabetic medications usually thiazolidinedione medications, normalizes aminotransferase levels and improves the parameters of inflammation.

Other lab abnormalities seen in NAFLD/NASH include abnormal sinusoidal deposition of immunoglobulin A. There is elevation of serum IgA and lowering of serum IgG/IgA ratio. The latter is associated with

more severe fibrosis. Anti nuclear antibodies are also found in about 25% of patients with NASH. Abnormal iron indices, including ferritin and transferrin saturation is present.

Imaging of the liver has also been used to assess the distribution of body fat in comparison with anthropometric measurements. Computerised tomographic measurement of abdominal visceral fat at the L4-5 intervertebral space, adjusted for age and sex is the most established technique. MRI and ultrasound have also been used to quantify body fat, especially central adiposity.

Ultrasonography:

In the liver, ultrasonography can detect the presence of hepatic steatosis by means of increased echogenicity and sound attenuation. The use of ultrasound as a screening tool for steatosis is limited because of the difficulty in differentiation steatosis from fatty infilteration,

misinterpretation of focal fatty sparing as a hypoechoic mass, and poor detection if the degree of steatosis is less than 30%. However for screening large population and in evaluation of pediatric patients for whom biopsy may be difficult, use of ultrasonography is common to diagnose 'presumed' NAFLD.

Computerised Tomography:

Unenhanced CT remains the optimal technique for imaging hepatic fat; the diagnosis depends on the attenuation differences between the liver and spleen.

Magnetic Resonance Imaging and Spectroscopy:

MRI has a less established role in imaging fatty liver. MR spectroscopy offers another means of assessing the degree of hepatic steatosis. It also

offers futuristic prospects of measuring metabolic parameters such as ATP levels in the liver and probably lipid peroxidation.

PATHOGENESIS OF NON-ALCOHOLIC STEATOHEPATITIS:

The development of NASH is likely to involve a 'two hit' mechanism in which the first hit is the development of steatosis (NAFL) and the second hit is the development of oxidative stress and lipid peroxidation (NASH).

Hyperinsulinemia is the most common association with fatty liver. Levels of both triglycerides (unsaturated fatty acids) and free fatty acids (mostly saturated) are higher in the liver of obese patients than that of controls of normal weight. Elevation of free fatty acids may play a central role in both fat loading of the liver and in the development of insulin resistance through inhibition of glucose transport, inhibition of glycogen synthesis and stimulation of gluconeogenesis.

Insulin resistance is characterized by a reduced sensitivity to insulin in target tissues, especially liver, muscle and adipose tissue. The expected manifestations of insulin resistance include increased hepatic glucose output (normally suppressed by insulin), decreased peripheral (muscle) glucose utilization and enhanced lipolysis. Abnormal insulin homeostasis has been demonstrated in both NASH and NAFLD. Sanyal et al, suggested that the predominant site of resistance in NAFLD and NASH is the peripheral fat and skeletal muscle as opposed to the liver.[31]Factors that may promote insulin resistance in NAFLD include fatty acid metabolism, cytokine metabolism and genetic variables.

Islet cell dysfunction is thought to be the turning point from latent hyperinsulinemia to the overt expression of diabetes in these patients. Although hyperinsulinemia in NAFLD is thought to potentiate liver disease through fat loading rather than to result from the liver problem. A similar feature of the islets to keep up with systemic needs may underlie the late development of overt diabetes in patients with NAFLD.

Lipid peroxidation reflects and imbalance between pro oxidant and anti oxidant substances (oxidative stress). It is a branching, chain reaction stimulated by a free radical attack on unsaturated fatty acids. Free radicals, which initiate the process, may be derived from mitochondrial, peroxisomal or cytochrome P450 fat metabolism with formation of superoxide, hydrogen peroxide and hydroxy radicals. The mitochondrion may be both an especially important source of reactive oxygen species and a target for injury resulting from lipid peroxidation. An additional source of injury in fatty liver may be endogenous production of ethanol caused by bacterial overgrowth.[32]

Mitochondrial morphologic abnormalities i.e., swelling, loss of cristae and development of crystalline inclusions are found in NASH. Although there is evidence of mitochondrial dysfunction in NASH, fatty acid oxidation appears preserved, as does ketoacid decarboxylation.

As in alcohol related liver disease, induction of CYP 2E1 in NASH, particularly in centrilobular distribution, has been described and may

further exacerbate oxidative stress and activation of cytokines. Microsomal CYP omega oxidation of fatty acids normally a minor pathway of fatty acid metabolism, may be a source of free radical generation in conditions of over abundant fat stores.

Leptin is a circulating protein encoded by the obesity gene (chromosome 7q31) and is produced primarily in white adipose tissue. Leptin has an effect on insulin and peroxisome proliferator- activated receptor gamma activity and the levels increase in cirrhosis. The primary role of leptin is to govern the satiety through the action at the hypothalamus- however obesity among humans is typically associated with paradoxically elevated leptin levels. Leptin has been variably implicated in the development of histological injury in NAFL, however the idea still remains controversial.

Elevation of cytokine levels, especially TNF alpha has been described occurring in NASH. Transformin Growth Factor Beta and interleukin 6 have been implicated as mediators of fibrosis in NASH in some studies but not in others. It is possible that cytokine abnormalities are only

secondary to lipid peroxidation and are not primarily pathogenic. The increased expression of intercellular adhesion molecule 1, inducible nitric oxide synthase and endoglin in more histologically severe NASH supports at least a major secondary role of cytokine mediated injury.

Peroxisomes are involved in numerous metabolic pathways, including synthesis of plasmalogens, bile acids, cholesterol and oxidation of very long chain fatty acids, branched chain fatty acids and dicarboxylic acids. Morphologic abnormalities with increased number but diminished size of microsomes have been found in fatty liver[33].

Peroxisomal fatty acid oxidation represents another potential source of reactive oxygen species, including superoxide and hydrogen peroxide, which form during peroxisomal oxidation of very long chain fatty acids and metabolism of dicarboxylic acids.

SECONDARY NON ALCOHOLIC STEATOHEPATITIS:

BARIATRIC SURGERY:

Weight reduction therapy played an important role in the recognition of NASH and NAFLD, owing to the unexpected exacerbation experienced by some patients after jejuno ileal bypass. Stimulation of TNF by bacterial endotoxin has been postulated as an etiologic factor.
Micro nutrient deficiency has also been proposed as a cause. Despite its historical association with NASH, weight loss surgery, especially gastric bypass remains a viable option in the care of some patients.

MEDICATION INDUCED CONDITIONS:

A number of medications have been implicated as a cause of steatohepatitis. Diltiazem, methotrexate and tamoxifen produce a histologic picture similar to NASH. The risk factors for tamoxifen and methotrexate induced hepatitis are similar to that of NASH. This finding

suggests a possible synergistic effect the drug in a patient prone to NASH.

Amiodarone has also been implicated as a cause of steatohepatitis. The use of amiodarone should not be undertaken without consideration of the high likelihood that many recipients have pre existing fatty liver because of shared risks between NASH and heart disease.

Acquired lipodystrophy associated with insulin resistance and steatosis and sharing features with multiple symmetric lipomatosis has been described as part of nucleoside analogue therapy for HIV virus infection. The syndrome appears to be increased in women, may manifest itself acutely, and can be associated with Reye – syndrome like clinical features, neuropathy, myopathy and pancreatitis. Mitochondrial disease is thought to be the underlying cause of this disorder.

PARENTRAL NUTRITION AND MALNUTRITION:

Liver disease, often with macrovesicular and microvesicular steatosis, is one of the most common and potentially severe side effects of total parentral nutrition. Phospholipidosis (fat laden cells in the sinusoidal space or portal tract) is also a common feature. Both the amount of lipid infusion and the composition appear to affect expression of liver disease in this setting. Choline deficiency probably plays a role in some patients. At the other end of the spectrum, fatty liver is a common finding in kwashiorkor, wherein export of lipid from the liver due to protein deficiency (diminished apoprotien B) is thought to be the primary mechanism. In both types of nutritional fatty liver, zone 1 (periportal) involvement may predominate. Potentially severe fatty infilteration of the liver can be seen in celiac disease and may be the presenting problem in this disease.

SOLVENTS AND INDUSTRIAL AGENTS:

A variety of medications and some industrial solvents have been implicated in the development of fatty liver. Some of them include, carbon tetrachloride, dimethyl formamide and perchloroethylene. Elements such as phosphorous and certain compounds such as ethyl bromide and ethyl chloride have been implicated. Synergy between exposure to these agents and disease progression in an obese or diabetic patient is yet to be established.

WILSON DISEASE:

Macrovesicular and microvesicular steatosis is a well known feature of Wilson's disease. It should be considered when a younger person has steatosis. Mitochondrial injury, mutations and premature oxidative aging have been described in patients with wilson's disease. These findings suggest a possible overlap, through mitochondrial dysfunction, with more typical NAFLD and NASH.

INHERITED METABOLIC DISORDERS:

Macro vesicular steatosis occurs in a variety of inherited metabolic diseases, most but not all, of which manifest themselves in childhood. Disorders include glycogen storage diseases, galactosemia, tyrosinemia, heterozygous hypobetalipoproteinemia and abetalipoproteinemia. The latter two disorders are characterized by impaired formation of very low density lipoproteins owing to decreased synthesis of apoprotein B. A number of lipid storage diseases such as cholesterol ester storage, Niemman pick's disease, Tay – Sach's disease and Gaucher's disease, are associated with excessive fatty infilteration of the liver with cholesterol esters, sphingolipids, phospholipids, sphingomyelin, gangliosides or glucocerebrosides. Manifestation as systemic diseases in infancy and the distribution differentiate lipid storage disorders from typical NAFLD and NASH.

THERAPY FOR NON ALCOHOLIC STEATOHEPATITIS AND NON ALCOHOLIC FATTY LIVER DISEASE:

There is no proven therapy for NASH. Furthermore, the criteria for clearly indicating who should undergo more aggressive therapy is not well defined.

Patients with simple steatosis probably need only observation with regard to liver disease, although associated conditions may warrant consideration of probable toxicity of common agents, such as, anti lipidemics, anti hypertensives, and anti diabetic medications. For patients with mild inflammation and no fibrosis, a less aggressive observational approach is required because the prognosis appears to be relatively good. A more directed therapy is required if fibrosis is present at biopsy.

DIETARY WEIGHT LOSS AND EXERCISE:

The most practical and most commonly recommended therapy is exercise, diet and weight loss. Weight loss may be associated with progression of liver disease, especially if the rate of loss is more than 1.6kg per week. It has been shown that the most effective conditioning exercise is that which just passes beyond the lactate threshold, a level usually associated with some degree of discomfort. Some studies have shown improvement in liver enzyme values, in histologic findings and degree of steatosis, however fibrosis was not significantly altered.[44]
If patients were subjected to drastic calorie reduction for 10 to 28 days, then the histological findings worsened.

WEIGHT REDUCTION SURGERY:

Roux en y gastric bypass procedure remains a popular weight loss procedure for overweight persons even though it carries a risk for hepatic decompensation. In patients undergoing sustained weight loss after this procedure, the biological markers for syndrome X, such as, plasma

glucose, insulin, fibrinogen, triglyceride, uric acid and ALT levels, are usually reduced. Liver biopsy showed a significant reduction in steatosis but a slight overall increase in inflammation, there usually is no significant change in fibrosis. Although this treatment is often effective, caution is warranted with surgical procedures for weight reduction, owing to the risk of decompensation even with more limited procedures.

URSODEOXYCHOLIC ACID AND CYTOPROTECTIVE AGENTS:

The potential benefits of UDCA may be derived from effects on mitochondrial membrane stability, improvement in blood flow or immuno modulation. Therapy with UDCA may improve ALT levels and steatosis grades but no significant change in AST levels, inflammation or fibrosis. Taurine, an amino acid, also normalizes the liver enzyme values in children.

ANTI HYPERLIPIDEMIC AGENTS:

Fibric acid derivatives have been used for hypertriglyceridemia. In general, their activity involves changes is lipoprotein metabolism, decreased delivery of free fatty acids to the liver, decreased release of VLDL from the liver, altered LDL metabolism and activation of PPAR α ligands. Treatment with gemfibrozil resulted in improvement in liver enzyme values. The over all effects of HMG Co A reductase inhibitors have not been well studied.

ANTI DIABETIC AGENTS:

Insulin resistance appears to be crucial in most patients with NASH, therefore therapy aimed at hyperinsulinemia, insulin resistance or overt diabetes seems reasonable.

Thiazolidinediones are ligands of PPAR γ that promote adipocyte differentiation. Use of these agents is associated with increased body

weight but decreased central adiposity, increased glucose transport and increased mitochondrial mass. They decrease the levels of some cytokines and inhibit inducible nitric oxide synthase. Troglitazone when used in the treatment of NASH, normalized liver enzyme values with no change in fibrosis. Troglitazone has shown benefit in the management of lipodystrophy.

Another diabetic agent that warrants consideration is, metformin (a biguanide agent), which decreases steatosis and improves histological findings in NASH. Metformin stimulates aerobic metabolism and increases lactate production in pre adipocytes under experimental conditions. Lactic acidosis, however, appears to be rare.

Acipimox is an inhibitor of lipolysis. It improves insulin sensitivity by lowering levels of free fatty acids. Its potential role in NASH is uncertain.

ANTI OXIDANTS AND NUTRITIONAL SUPPLEMENTS:

Suppression of lipid peroxidation, TNF, and collagen gene expression have been reported with the use of vitamin E.
N acetyl cysteine, which is converted to glutathione in the liver, improves liver enzyme values.

Betaine, is a methyl donor in an alternative pathway for remethylation of homocysteine to methionine. S-adenosyl- methionine (SAMe) promotes conversion of phosphatidylethanolamine to phosphatidylcholine (lecithin), which promotes export of fat from the liver as VLDL. The use of this agent in NASH causes substantial improvement in biochemical values and relief of several histologic abnormalities, including steatosis, inflammation and fibrosis.

Silymarin, the active component of milk thistle extract, is an over the counter drug that has been found to decrease the expression of CYP3A4 and to decrease mitochondrial respiration in hepatocyte culture.
Lazaroids, or 21 amino acid steroids, are anti oxidants. The above two

drugs have not been studied in the management of NASH but warrant consideration.

LIVER TRANSPLANTATION:

Transplantation in the care of advanced NASH often is complicated by the presence of co morbid conditions related to obesity, diabetes and hyperlipidemia. Recurrence of liver disease is another concern. Many reports have documented the recurrence of NASH and NAFLD after transplantation.

Immunosuppression may play a role in the recurrence of NAFLD. Steroid therapy may promote fatty change and cyclosporine interacts with the mitochondrial transition pore, which regulates the electrochemical gradient across the mitochondrial membrane.

Steatosis in donor livers is associated with relatively poor graft function. This likely reflects abnormal mitochondrial function and disturbed ATP homeostasis. Therefore pre operative liver biopsy on prospective donors

who are at high risk (increased BMI) is needed even if results of imaging studies are normal, in order to detect steatosis.

MATERIALS AND METHODS

The study was conducted in Govt. Royapettah Hospital between March 2004 to March 2007. The following are the patients' inclusion and exclusion criteria:

INCLUSION CRITERIA:

1. Presence of diabetes mellitus (types 1 or 2) of any duration.

EXCLUSION CRITERIA:

1. Consumption of alcohol
2. Seropositivity to HIV ELISA
3. Seropositivity of anti HCV antibody
4. Patients on drugs that are proven to cause steatohepatitis (steroids, amiodarone, oral contraceptive pills and other estrogen containing preparations.

A total of 75 diabetics(both type 1 and type 2) were studied during this period. Both inpatients and outpatients were included in the study. The study group consisted of about 15 males and 60 females, between the age groups of 19 – 73 yrs, the average age being 51.88 yrs. The duration of diabetes in these patients ranged between 0 to 20 yrs, with the average duration being 5.17 yrs.

All the above patients were screened for HIV and HCV and were negative for both. The following investigations were done on these patients:

- Liver function test
- Lipid profile
- Ultrasound abdomen
- Random blood sugar

The patient's weight and height were measured and BMI calculated. A BMI >25 was considered overweight.

Waist hip ratio was also measured to look for central obesity.

If the ultrasound showed evidence of fatty liver, with or without the elevation of transaminases, a presumptive diagnosis of NAFLD was made.

The data were collected and analysed for the following:

- Prevalence of NAFLD
- Association between lipid profile and presence of NAFLD
- Relationship between central obesity and NAFLD.

RESULTS

Among the 75 diabetics who were studied, fatty liver was found in 31 patients (41.33%).

No. of patients with fatty liver	No. of patients without fatty liver
31 (41.33%)	44

The number of males with fatty liver were 2 (2.6%) and females 29(38.6%)

Sex	Fatty liver present	Fatty liver absent
Male	2 (2.6%)	13
Female	29 (38.6%)	36

The number of patients with fatty liver who had central obesity (waist hip ratio >1) – 23 (74.19%). All the patients with fatty liver had central obesity (waist hip ratio >1 in males and >0.85 in females)

Waist hip ratio >1	Waist hip ratio <1
23 (74.19%)	8 (25.8%)

The number of patients who had increased triglycerides >180 among patients with fatty liver 28 (90.3%)

No. of patients with ↑ TGL	No. of patients with normal TGL
28 (90.3%)	3

No. of patients who were overweight among the persons detected to have fatty liver – 21 (67.74%)

No. of patients with normal BMI among the persons with fatty liver – 10 (32.2%)

No. of patients with BMI >25	No. of patients with BMI <25
21 (67.74%)	10 (32.2%)

No. of patients with increased cholesterol (>200 mg%) among patients with fatty liver – 20 (64.5%)

Patients with cholesterol >200	Patients with cholesterol <200
20 (64.5%)	11 (35.48%)

All the patients with ultrasound evidence of fatty liver showed, marginally elevated transaminases and occasionally of serum alkaline phosphatase. There was no alteration in the serum protein or albumin globulin ratio.

DISCUSSION

The prevalence of fatty liver in this study was found to be 41.3%. According to a study conducted by Daad H. Akbar, the prevalence of NAFLD was found to be 55%.[48] According to another study conducted by Gupta P et al the prevalence of NAFLD, by ultrasound examination, was found to be 49%.[46]

Among the patients with NAFLD the percentage of patients who were overweight was 67.74%. Wanless and Lentz found mild to severe steatosis in approximately 70% of obese patients and 35% of lean patients.[20]
Garcia Monzon et al found NASH in 69% whereas 22% had simple steatosis and only 8% had normal biopsy findings.[47] In another study the presence of NAFLD was highest among obese patients, with BMI of 30 +/- 5.5 kg/m^2.[46] However, in another study there was no significant difference in body mass index among patients with NAFLD.[48]
NASH can exist with only non specific symptoms for years in obese patients before manifesting itself either incidentally or with complications of cirrhosis or portal hypertension.

The prevalence of fatty liver was found to be higher among women (38.6%) than men. Many studies have found the presence of fatty liver to be higher in women.[12,48]

NAFLD and NASH have been described in patients without the classic risk factors of obesity, diabetes and overt hyperlipidemia. It has been described in patients with central of visceral adiposity in a study conducted by Bacon BR et al.[47] In another study, fatty liver was strongly correlated with visceral adipose tissue.[48]In this study the percentage of patients with central obesity among patients with fatty liver was 100% and those with a waist hip ratio of >1 was 74%.

The no. of patients with increased triglycerides and cholesterol was found to be 90.3% and 64.5% respectively. As mentioned earlier two thirds of patients with hypertriglyceridemia and one third of patients with hypercholesterolemia have fatty liver.[26] In another study, among patients with obesity and fatty liver, approximately 20% have some type of previously identified hyperlipidemia.[48] In other studies, fatty liver was strongly correlated with the degree of dyslipidemia, especially the level of

triglycerides. Hypertriglyceridemia was identified as an important risk factor in the development of NAFLD and NASH, it also correlates well with the histological severity of the disease.[46,47,48]

In summary, obesity and type 2 diabetes are the best characterized risk factors, with older age and presence of hypertriglyceridemia, are predictors of the severity of underlying histologic changes. Many lean patients with fatty liver have truncal or central adiposity. The prevalence of NAFLD is more in women than men. Only 10% of consecutively examined obese patients have normal results at liver biopsy. Apporximately 5% have cirrhosis and 85% have steatosis. One third of the latter have NASH.

CONCLUSION

- The prevalence of non-alcoholic fatty liver disease was 41.3% and it was present mainly in patients with type 2 diabetes mellitus.
- It occurred more commonly in women (38.66%) than men.
- The occurrence of non-alcoholic fatty liver was found to be higher in patients who were overweight/ obese and in those with central obesity.
- 90.3% of the patients with fatty liver had dyslipidemias (especially hypertricglyceridemia.

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PROFORMA

NAME:

AGE:

SEX:

OP/IP NO.:

WEIGHT (IN KG):

HEIGHT (IN CM):

BODY MASS INDEX:

WAIST (IN CM):

HIP (IN CM):

WAIST HIP RATIO:

DIAGNOSIS:

DURATION OF DIABETES:

DRUGS TAKEN BY THE PATIENT FOR

DIABETES AND OTHER COMORBID

CONDITIONS:

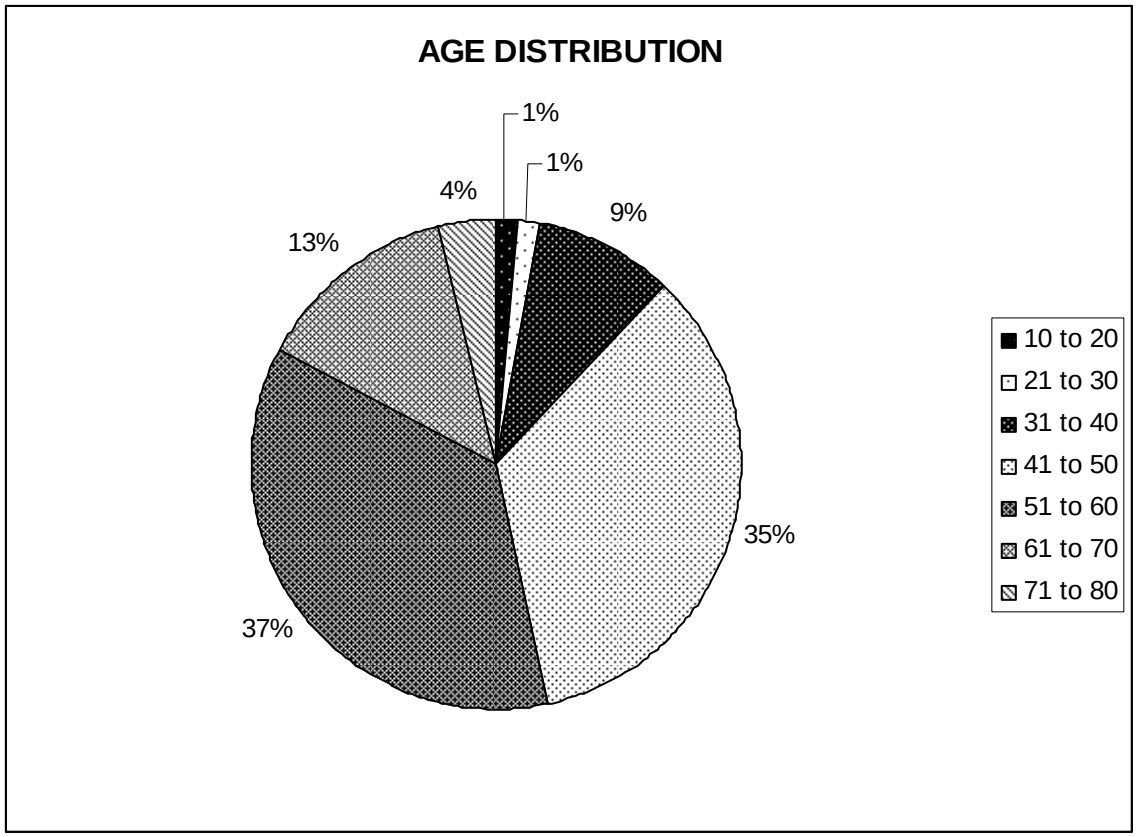
LFT:

LIPID PROFILE:

ULTRASOUND ABDOMEN:

KEY TO MASTER CHART

• M	Male
• F	Female
• OP	Out patient
• IP	In patient
• BMI	Body mass index
• WHR	Waist hip ratio
• DM durn	Diabetes mellitus duration
• T.Bil	Total bilirubin
• AST	Aspartate amino transferase
• ALT	Alanine amino transferase
• SAP	Serum alkaline phosphatase
• T.Pro	Total protein
• T.Chol	Total cholesterol
• HDL	High density lipoprotein
• LDL	Low density lipoprotein
• VLDL	Very low density lipoprotein
• USG abd	Ultrasonogram abdomen
• RBS	Random blood sugar
• MF	Metformin
• G	Glibenclamide
• Gl	Gliclazide
• Gm	Glimipride
• CAD	Coronary artery disease
• CKD	Chronic kidney disease
• PT	Pulmonary tuberculosis
• Ch’it is	Cholecystitis
• COAD	Chronic obstructive airway disease
• Gbstone	Gall bladder stone
• CA brst	Carcinoma breast
• CVA	Cerebro vascular accident
• TIA	Transient ischemic attack
• Ren calc	Renal Calculi
• Fil scrotm	Filarial scrotum
• Ing hern	Inguinal Hernia
• Hyd’coele	Hydrocoele
• GUTB	Genito urinary tuberculosis
• DM	Diabetes mellitus type 2
• DM type 1	Diabetes mellitus type 1


AGE DISTRIBUTION
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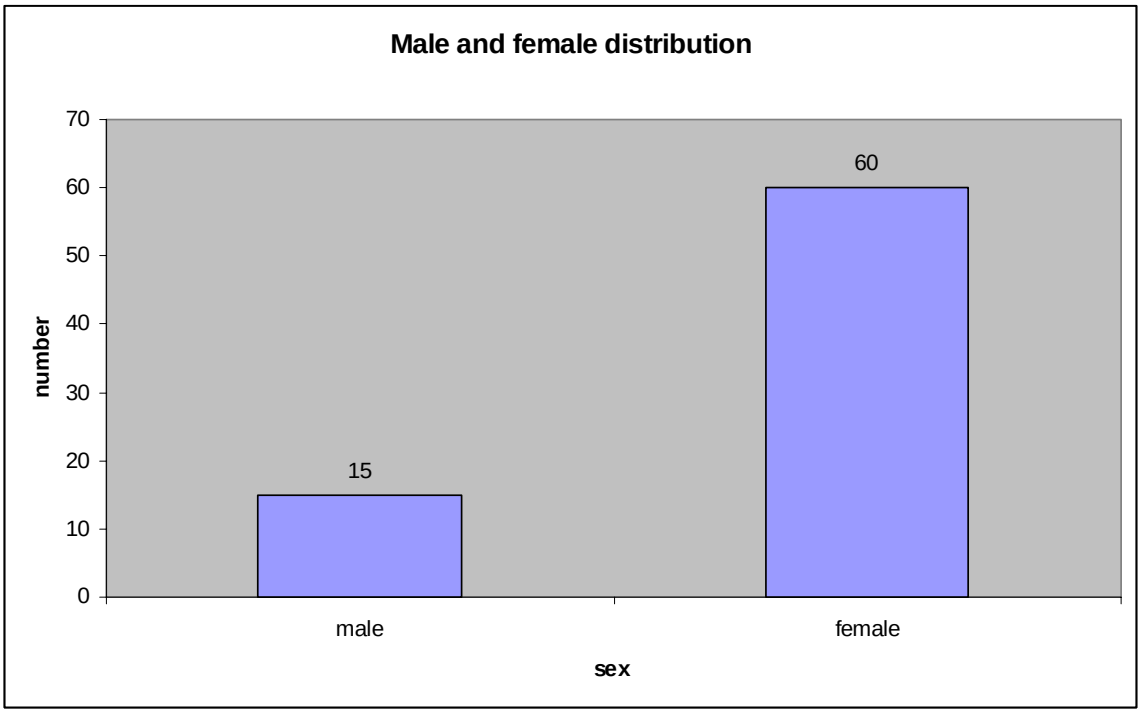
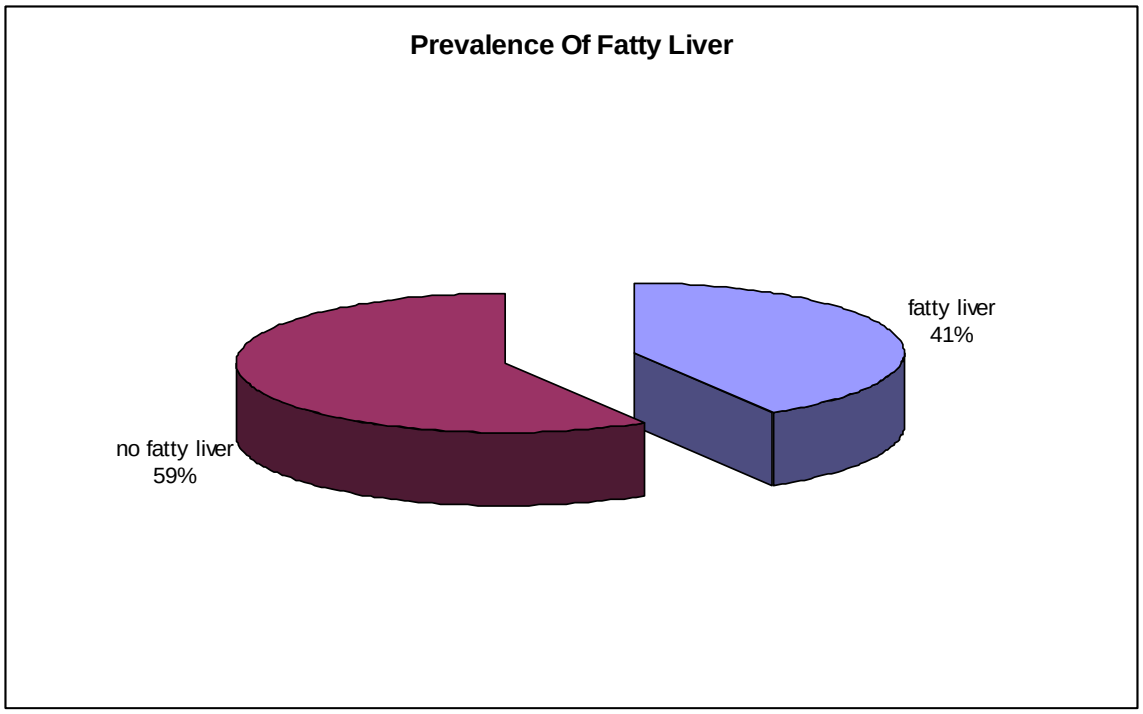
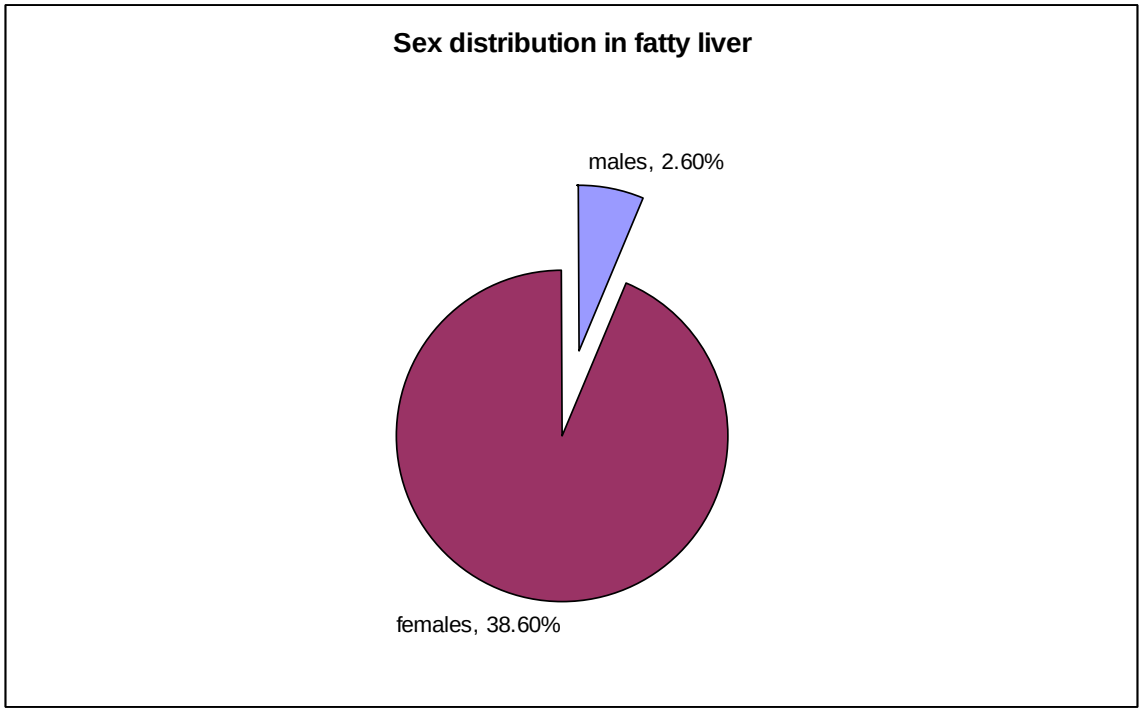
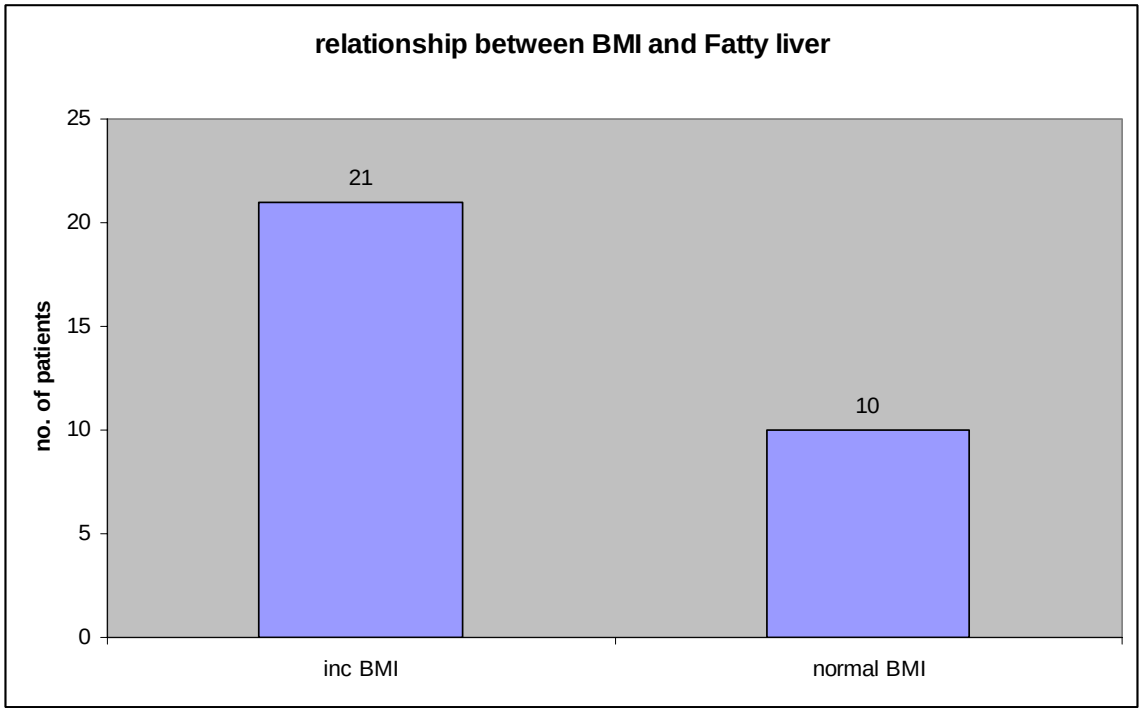
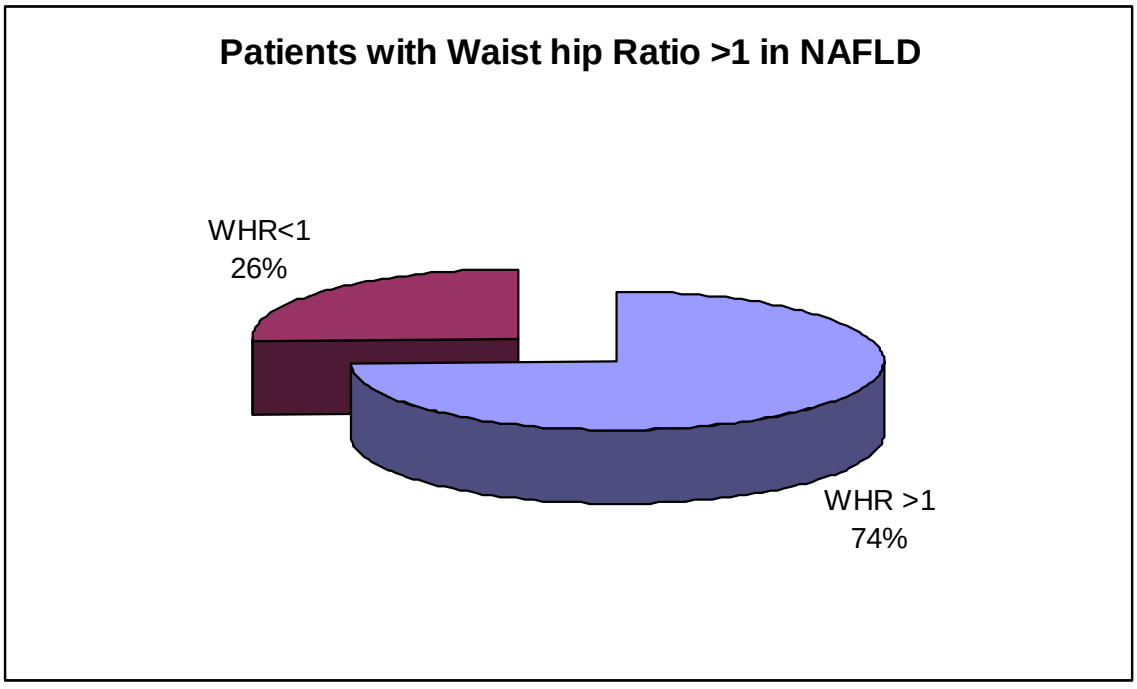

Male and female distribution
70
60
50
40
30
20
10
0
number
60
15
male
female
sex


Prevalence Of Fatty Liver
fatty liver
41%
no fatty liver
59%


Sex distribution in fatty liver
males, 2.60%
females, 38.60%


relationship between BMI and Fatty liver
no. of patients
25
20
15
10
5
0
21
10
inc BMI
normal BMI


Patients with Waist hip Ratio >1 in NAFLD
WHR<1
26%
WHR >1
74%