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A Study of 100 Cases of Non-Alcoholic Fatty Liver Disease (NAFLD) in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: NAFLD (Non-alcoholic Fatty Liver Disease) is an increasingly important chronic liver disease next to alcoholic liver disease ranging from Steatosis, steatohepatitis to cirrhosis. Insulin resistance and oxidative stress play important roles in etiopathogenesis of this disease.

Objectives: To find out prevalence of NAFLD in patients with type 2 DM (Diabetes Mellitus).

Materials and Methods: This is cross sectional one year study of 100 patients with type 2 DM of medicine department in tertiary care hospital to know the association of NAFLD with type 2 DM. Case history, examination, BMI, & investigations like RBS, FBS, PP2BS, HBA1C, liver function tests, lipid profile, ultrasonography of abdomen were done to evaluate the association.

Results: Out of 100 patients in study with type 2 DM, 64 patients had NAFLD, so higher prevalence (64%) in type 2 DM patients, Out of 64 patients with NAFLD higher prevalence (37.5%) in 50-59 years age group, more in male (65.62%) as compare to female (34.38%), higher association of CAD (57.81%) & Obesity (87.5%) & metabolic syndrome (90.62%) among NAFLD patients.

Conclusion: Higher prevalence of NAFLD in type 2 DM population. So, a positive correlation between hyperinsulinemia, abnormal glucose tolerance and NAFLD.

Keywords: Cirrhosis, Fibro scan, Insulin Resistance, Metabolic Syndrome, NASH (Non-alcoholic Steatohepatitis).

Introduction

NAFLD represents spectrum of disease, characterized histologically by excessive accumulation of hepatic fat in the absence of significant alcohol consumption, with or without inflammation, varying fibrosis, and cirrhosis.[1] NAFLD includes both non-alcoholic fatty liver (NAFL), and NASH, with or without varying degrees of fibrosis and cirrhosis.[2] NAFLD has four histological stages: (I) Fatty infiltration of the liver; (ii) Fatty infiltration plus inflammation; (iii) Fatty infiltration with ballooning degeneration; (iv) Fatty infiltration with lesions similar to alcoholic hepatitis and sinusoidal fibrosis, poly morph-nuclear infiltration with or without Mallory hyaline. NASH is the name given to the third and fourth stage.[3] NAFLD is more benign condition while NASH is more likely to progress to cirrhosis (End Stage Liver Disease) and hepatocellular carcinoma (HCC).

A disease practically unheard of 4 decades ago, is now considered as one of the most common causes of chronic liver disease in industrialized world.[4] Moreover with increasing incidence and prevalence, the perception of NAFLD being a benign condition of little clinical significance is rapidly changing. The overall prevalence of NAFLD in western countries

varies from 15-40% and in Asian countries from 9 to 40%. In India too, NAFLD is emerging as an important cause of liver disease. Epidemiological studies suggest the prevalence of NAFLD to be around 9-32% in general Indian population, with a higher incidence amongst overweight/obese and diabetic/prediabetic patients.[5,6]

Metabolic syndrome and associated co morbidities like type 2 DM, obesity and dyslipidaemia are predisposing factors of NAFLD; and prevalence of NAFLD has increased parallel to these epidemics. The association of type 2 DM with micro and macro vascular complications is well established, but the association of type 2 DM with NAFLD as a major complication has been recently recognized. Approximately 70% of type 2 DM patients have a fatty liver and they also appear to have more severe forms of the disease including NASH and fibrosis, with standardized mortality rate for death greater than that for cardiovascular disease (CVD) [7, 8]. There is evidence that type 2 DM patients with NAFLD are at higher risk of developing cirrhosis compared to non-diabetic patients[11, 12].

In this study, we have estimated the prevalence of NAFLD on ultrasonography in patients with type 2 DM and correlated it with coronary artery disease (CAD) and coronary risk factors. We found that diabetic patients with NAFLD have higher prevalence of CAD, obesity, poor glycaemic control, dyslipidaemia. This correlation of NAFLD with coronary artery disease was present also on multivariate analysis.[1]

Originally, the term NASH was first introduced by Ludwig and co-workers in 1980, when they described the histological findings that occurred in obese, diabetic patients (mainly women) who denied alcohol use.[9]

NAFLD is operationally said as fatty liver (FL), i.e., an accumulation of lipids inside the hepatocytes exceeding 5% of the weight of the liver, without hepatitis B virus or hepatitis C virus Infection and in the absence of 'excessive' Ethanol intake (conventionally Defined as an intake of ethanol >20 g/day for women and >30g/day for men). Other non-alcoholic and non-viral causes of FL that should be excluded.

Pathogenesis:

'Two hit' model of NASH pathogenesis it is proposed that steatosis is the first hit which makes the liver more susceptible to subsequent hits such as inflammation, lipid peroxidation and the generation of reactive oxygen species.[7] The degree of insulin resistance has been shown to correlate with the presence of more advanced liver disease and reducing insulin resistance by pharmacological agents or lifestyle changes, improves steatosis. This supports the proposal that insulin resistance is causative for steatosis and not secondary. Peripheral insulin resistance is defined as decreased insulin mediated uptake of glucose in peripheral tissues such as skeletal muscle and adipocytes, and a progressive decrease of glucose utilization by the skeletal muscles occurs with the escalation of hepatic steatosis to NASH[7]. The second hit is hepatocellular injury that results from oxidative stress, lipid peroxidation and direct cellular toxicity from FFAs. Mechanisms proposed includes role of FFAs, CYP2E1, PPAR-ALPHA, pro inflammatory markers, mitochondrial dysfunction, etc.

The main pathogenic mechanism of NAFLD is insulin resistance in the liver and extra hepatic tissues such as adipose tissue and skeletal muscle which act synergistically leading to systemic inflammation which causes the release of pro atherogenic and nephrotoxic factors. There is an increased flux of free fatty acids (FFAs) to ectopic tissues due to an increased rate of lipolysis in the dysfunctional adipose tissue causing the muscle and liver to develop insulin resistance and apoptosis. Thus, the “lipotoxic state” in NASH results in hepatocyte necroinflammation. There are three sources of triacylglycerol (TAG) which tends to accumulate in the liver: 59% of it is from circulating FFAs; de novo lipogenesis (the process in which carbohydrates are converted to lipids) contributes to 26%; and the rest 14% is from the diet. FFAs entering the portal circulation has one of the three fates: either to undergo ß-oxidation; to undergo re esterification to TAG and get fluxed out as very low-density lipoprotein (VLDL); or to get stored in the liver after re-esterification. De novo lipogenesis is further enhanced by insulin resistance. There is reduced rate of glycogen synthesis with increased rate of gluconeogenesis in NAFLD. The increase in intrahepatic glucose and resultant product of glycolysis pyruvate act as substrates for de novo

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lipogenesis which in turn increases the production of acetyl-CoA, which gets converted to malonyl-CoA contributing to de novo lipogenesis, instead of allowing it to enter the citric acid cycle. All the above contribute to hepatic steatosis. Oxidative stress, mitochondrial dysfunction, and circulating cytokines are the contributing factors for transition from simple steatosis to NASH, which then progresses to fibrosis.

NAFLD is an ectopic fat accumulation which is associated with increased secretion of hepatokines, increased gluconeogenesis, decreased glycogen synthesis and inhibition of insulin signalling. Adipose tissue inflammation is crucial in NAFLD pathogenesis and evidence suggesting that dysbiosis of the gut micro biota also plays a major key role in development and progression of NAFLD. This is mainly because of the increased intestinal absorption of bacterial products, such as short-chain fatty acids (e.g., butyrate, propionate and acetate), lipopolysaccharide and endotoxins. Although obesity is strongly associated with hepatic steatosis, excess body fat accumulation is not 'sine qua non' for developing NAFLD. In fact, patients with lipo dystrophy have marked insulin resistance and commonly develop hepatic steatosis and T2DM, strongly suggesting that it is not body fat mass per se that is important, but it is adipose tissue dysfunction that is a key contributor to the pathogenesis of NAFLD.

Role Of Ceramides:

In the liver ceramides can accumulate into the cells via three main routes:

1) Hydrolysis of the membrane phospholipid sphingomyelin, which is coordinated by the enzyme sphingomyelinase;

2) De novo synthesis from long chain fatty acids such as palmitate and 18 serine; and

3) 'Salvage' pathway that utilizes sphingosine and forms ceramide. Ceramide plays an important role in causing insulin resistance.

They induce endoplasmic reticulum stress, leading to the activation of c-Jun N-terminal kinases and NF-kB, which are two major regulators of inflammatory pathways that inhibit phosphorylation of insulin receptor substrate-1 (IRS-1) by inhibiting PKB (phosphor kinase B), potentially aggravating hepatic insulin resistance and increasing intra-hepatic cytokine production. Synthesis of lipids such as di acyl glycerol (DAGs) is intimately related to hepatic production of inflammatory cytokines [e.g. Tumour necrosis factor-a (TNF-a), interleukin-6 (IL-6)], and procoagulant factors [e.g., factor VIII, plasminogen activator inhibitor-1 (PAI-1)].

Till date, it is unclear whether improvements in NAFLD may ameliorate risk of T2DM or improve glycaemic control in people with NAFLD who have developed T2DM, but it is plausible that resolution of liver fat and improvements in liver lipid metabolism might modify the risk of T2DM via a liver-specific effect. Such a liver-specific effect could be mediated by alteration in the secretion of multiple hepatokines or inflammatory cytokines that influence risk of diabetes. In NAFLD, secretion of diabetogenic hepatokines, such as retinol binding protein (RB)-4, fetuin-A, fibroblast growth factor (FGF)-21; or inflammatory biomarkers such as C-reactive protein (CRP), TNF-a and IL-6 may directly affect risk of incident T2DM by adversely affecting hepatic gluconeogenesis, glycogen synthesis and insulin signalling. TNF-alpha influences steatosis by stimulating the release of FFAs from adipocytes into the liver. TNF-alpha may directly induce apoptosis of hepatocytes promoting activation of hepatic stellate cells, stimulating fibrosis. Leptin potentially may stimulate platelet-derived growth factor, ultimately leading to hepatic stellate cell proliferation resulting in fibrosis.

Signs, Symptoms & Diagnosis:

Most common- asymptomatic with elevated liver enzymes (particularly ALT).

Other symptoms are- malaise, fatigue, jaundice/ icterus, right upper quadrant or diffuse abdominal discomfort, pedal oedema, abdominal distension, hematemesis, hepatic encephalopathy. Hepatomegaly is commonly found on clinical examination. When cirrhosis appears, stigmata of chronic liver disease, such as spider angioma, ascites, splenomegaly, lipodystrophy, hard liver border, palmar erythema, asterixis, can be present[12]. Patients might complain of pruritus, or they might present with a complication of portal hypertension (e.g., ascites, variceal bleeding, or encephalopathy). Most patients have associated features of the metabolic syndrome: obesity (47%-90%), diabetes mellitus (28%-55%)

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and variable incidences of hyperlipidaemia (4%-92%) and hypertension13. It can also be identified incidentally on imaging or, less often, on liver biopsy done for other reasons. Clinical evaluation includes a careful history and physical examination. It is particularly relevant to inquire about excess alcohol consumption - defined as >30 g/day for men and >20 g/day for women within the past 5 years.

Liver profile: AST (SGOT/ Aspartate Aminotransferase), ALT (SGPT/ Alanine Aminotransferase), Total and direct bilirubin, Serum albumin, PT/aPTT/INR. Mild to moderate elevation of serum aminotransferase levels is most commonly found (mean range, 100-200 IU/L). Generally, the ratio of AST to ALT is <1, but this ratio increases as fibrosis advances. Liver enzyme levels are normal in a large percentage of patients with NAFLD; normal enzyme levels do not exclude the presence of advanced disease. Serum alkaline phosphatase and gamma-glutamyl trans peptidase levels may also be mildly abnormal.

For Diabetes: Fasting serum glucose, random plasma sugar, PP2BS (Post prandial blood sugar), HbA1C (Glycosylated haemoglobin) can be done.

Scores like AST/ALT ratio, BARD score, FIB-4 score, HAIR score and BAAT score can be used to predict prognosis. Biomarkers like CK-18 (cytokeratin- 18) & CK-8, CRP, Adiponectins, TNF-alpha, IL-6 etc. can be used.

Imaging: A liver ultrasound: examination is useful for confirming steatosis. Fatty infiltration of the liver produces a diffuse increase in echogenicity (a bright liver) and vascular blurring. Unfortunately, ultrasound cannot rule out steatohepatitis or fibrosis, and its sensitivity drops sharply when <30%o of hepatocytes contain fat droplets. It also has low accuracy in obese patients.

Hepatic elastography/ fibro scan: It is a non-invasive measurement of hepatic fibrosis by measuring liver stiffness, which is increased with increased fibrosis. Fibrotic livers have less elasticity due to the fibrous tissue deposition in the hepatic parenchyma. 'Liver stiffness measurement' (LSM) using pulsed-echo ultrasound as a surrogate marker of fibrosis.

Other investigations that can be used are- CT scan, MRI, MRS, ARFI (Acoustic Radiation Force Impulse) with use of B-scan USG, Scintigraphy using Tc-99m sulphur colloid scan. Liver biopsy is the gold standard for diagnosis. The distinction between pure fatty-change and steatohepatitis can only be made histologically. This distinction is important because NAFLD has a benign prognosis, whereas NASH progresses toward cirrhosis. Because of the risk of NASH in patients suspected to have fatty liver, it could be argued that all patients should be offered a liver biopsy to stage the disease[13]. Histological diagnosis of steatohepatitis relies on a constellation of lesions that include ballooning of hepatocytes (hepatocyte injury), perisinusoidal fibrosis and a mixed lobular inflammatory infiltrate.[10]

Grades Of Nafld:

Macro Vesicular Steatosis

1. Grade 0: No steatosis
2. Grade 1: < 33% steatosis
3. Grade 2: 33-66% steatosis
4. Grade 3: > 66% steatosis

Necroinflammatory Activity

1. Grade I (mild) steatosis up to 66%; occasional ballooned hepatocyte (mainly zone 3); scattered intra-acinar neutrophil (PMN) lymphocytes, no or mild portal inflammation.
2. Grade 2 (moderate): steatosis of any degree; obvious zone-3 ballooning degeneration; intra-acinar PMNs; zone-3 perisinusoidal fibrosis may present mild to moderate, portal and intra-acinar inflammation
3. Grade 3 (severe) pan acinar steatosis; widespread ballooning; intra-acinar inflammation; PMNs associated with ballooned hepatocytes, mild to moderate portal inflammation.

Natural History Of Non-Alcoholic Fatty Liver Disease:

NAFLD is a slowly progressive disease; however, in 20%, it progresses rapidly. Progression in NAFL to fibrosis Stage 1 is every 14 years and every 7 years in NASH. Cirrhosis and liver failure occurs in 11%–20% in NASH patients over 10–15 years. There is a 2.2-fold increase in overall mortality in NAFLD with the most common cause of death being cardiovascular disease. Patients with NASH (but not NAFL) have an increased liver-related mortality rate with decompensated liver failure and HCC corresponding to 2%. The mortality rate of T2DM

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patients due to cirrhosis is more than twice the general population and patients with both NAFLD and T2DM. Furthermore, they tend to have a poor prognosis with higher rates of cirrhosis and mortality.

Treatment options includes lifestyle modifications (like weight reduction, diet modification, and exercise), treatment of obesity & metabolic syndrome, insulin sensitizers (ex. metformin). Doubtful benefits of antioxidants (vitamin E), pentoxyfylline, betaine, N-acetyl Cysteine, L-Carnitine.

Aims And Objectives:

To find out the prevalence of NAFLD by ultrasonography in person with type 2 DM. To correlate NAFLD with coronary risk factors by using pathophysiological tests in type 2 DM .To assess the relationship between Body Mass Index & Obesity and NAFLD in Type 2 DM.

Materials And Methods: This is cross sectional one year study of 100 patients with type 2 DM of medicine department in G. G. Hospital, Jamnagar, Gujarat to know the association of NAFLD with type 2 DM. Patients were selected on basis of inclusion and exclusion criteria and predesigned pro forma for data collection.

Inclusion Criteria: Patients diagnosed to have type 2 diabetes mellitus, belonging to both sexes & with age of more than 35 years.

Exclusion Criteria: Patients with history of alcohol consumption for any duration of time, persons with previous history of jaundice, ascites & signs of liver cell failure, persons having known hepatic disease, HBs antigen or anti-HCV positivity & ingestion of hepatotoxic drugs were excluded.

Methodology: Detailed history, physical examination, BMI Calculation, CBC, RBS, FBS, PP2BS, HBA1C, ECG, USG ABDOMEN, LFT, RFT, S.Albumin, Urine Albumin, Fundus Examination used during study.

The selected patients were briefed about the nature of the study and gave informed consent.

A detailed history of CAD risk factors like smoking, hypertension, physical activity and treatment taken & ECG was recorded.

Body mass index was calculated based on formula:

$BMI = Weight\ (kg) / Height^2\ (meter)$

All patients underwent USG abdomen to detect fatty changes in the liver, performed by experienced radiologist, using a high-resolution B- mode ultrasonography system (TOSHIBA) having an electric linear transducer mild frequency of 3-5 MHz On USG fatty liver was defined as parenchymal brightness, liver to kidney contrast, vessels blurring, and narrowing of the lumen of the hepatic veins in the absence of finding suggestive of chronic liver disease.

USG criteria as:

1. **Grade 1** (mild steatosis): slightly increased liver echogenicity with normal vessels and absent posterior attenuation
2. **Grade 2** (moderate steatosis): moderately increased liver echogenicity with partial dimming of vessels and early posterior attenuation
3. **Grade 3** (severe steatosis): diffusely increased liver echogenicity with absence of visible vessels and heavy posterior attenuation

The study group was divided into 2 subgroups:

1) NAFLD: patient with USG evidence of fatty changes in the liver

2) Non-NAFLD: patients without any USG evidence of fatty changes in the liver.

Statistical Analysis:

Data entry was done in Excel file. While statistical analysis was done using IBM SPSS 20 statistical software package. Data were presented using descriptive and inferential statistics in the form of frequencies and percentages for categorical variables. Qualitative categorical variables were compared using chi- square test. Statistical significance was considered at p-value <0.005.

Results:

In Our Study, We Include 100 Patients with Age of > 35 years with type 2 diabetes mellitus among which 66 were males and 34 were females.

32 patients were hypertensive.

53 patients were having coronary artery disease.

83 were having metabolic syndrome.

88 were obese patients & 12 were non obese.

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64 patients were having ultrasonography evidence of fatty liver & 36 patients weren't having ultrasonography evidence of fatty liver.

Our results shows that the higher prevalence 24 (37.5%) patients were in age group 50-59 Years. The mean age of NAFLD patients were 51.81± 9.87(see table 1).

Our Result Shows prevalence of NAFLD was higher in Male 42 (65.62%) as compare to Female 22 (34.38%). NAFLD is more common among Male than Female in all age group due to protecting nature of estrogen in Female (see table 2)

In this study prevalence of NAFLD was present in 64% DM II patients (see figure 1)

Our results shoes prevalence of CAD was significant in NAFLD group (57.81%) as compare to non NAFLD group (44.44%) Our result shows hypertension present in 22 (34.67%) NAFLD patients and 10 (27.66%) in non-NAFLD. In this study NAFLD was not correlated with hypertension in diabetes patients (see table 3) (see figure 2)

Our result showed central obesity in 56 (87.5%) NAFLD Patients.

In our Study BMI > 25 kg/m^2 was present in 59 (92.18%) patients of NAFLD group and in 35 (91.22%) patients of Non-NAFLD group (see table 4)

In this study, metabolic syndrome, as defined as ATP III criteria, was present in 58 (90.62%) patients study group. Prevalence of metabolic syndrome was nearly significantly in NAFLD subgroup compares to non-NAFLD (90.62% vs. 69.44%) (p=0.0621) (See table 5)

Using a Cut off level of HbAlc > 7% as a measure of poor glycaemic control. In our Study elevated the HbAlc level > 7% was present in 61 (95.31%) patients of NAFLD group and in 31 (86.11%) patients of Non-NAFLD. The mean comparison between HbAlc level of our study 7.96 ±1.12 mg/dl in NAFLD group and 7.87 ± 1.31 mg/dl in Non-NAFLD Group were not significant as (p=0.7177), this suggests prevalence of NAFLD was higher in uncontrolled DM..

TABLES:

TABLE 1: AGE DISTRIBUTION OF NAFLD PATIENTS

AGE (YRS)	**Nonalcoholic Fatty Liver Disease**	
	YES	**NO**
35-39	08 (12.50%)	03 (08.33%)
40-49	16(25.0 0%)	13(36.11%)
50-59	24 (37.50%)	11(30.55%)
60-69	14(21.87%)	9 (25.00%)
>70	2(03.12%)	0
Total	64	36

TABLE 2: SEX WISE DISTRIBUTION OF NAFLD PATIENTS

SEX	Nonalcoholic Fatty Liver Disease	Non- Nonalcoholic Fatty Liver Disease
MALE	42 (65.62%)	24 (66.66%)
FEMALE	22 (34.38%)	12 (33.33%)
Total	64(100%)	36 (100%)

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TABLE 3: CORRELATION OF NAFLD WITH OTHER COMORBID CONDITION

CO MORBID CONDITION		Nonalcoholic Fatty Liver Disease N=64	Non- Nonalcoholic Fatty Liver Disease N=36
Hypertension	Present	22 (34.37%)	10 (27.77%)
	Absent	42 (65.62%)	26 (72.22%)
CAD	Present	37(57.81%)	16 (44.44%)
	Absent	27 (42.18%)	20 (55.55%)

TABLE 4: CORRELATION OF NAFLD WITH BMI

BMI kg/m^2	Nonalcoholic Fatty Liver Disease	Non- Nonalcoholic Fatty Liver Disease	P Value
>25	59 (92.18%)	35 (97.22%)	0.8344
<25	05 (07.82%)	01 (02.77%)	
Total	64 (100.0%)	36 (100.0%)	

TABLE 5: CORRELATION OF NAFLD WITH METABOLIC SYNDROME

Metabolic Syndrome	Nonalcoholic Fatty Liver Disease	Non- Nonalcoholic Fatty Liver Disease
YES	58 (90.62%)	25 (69.44%)
NO	06 (09.37%)	11 (30.55%)
Total	64 (100.0%)	36 (100.0%)

FIGURES:

Figure 1: Prevelance Of Nafld In Type 2 Dm

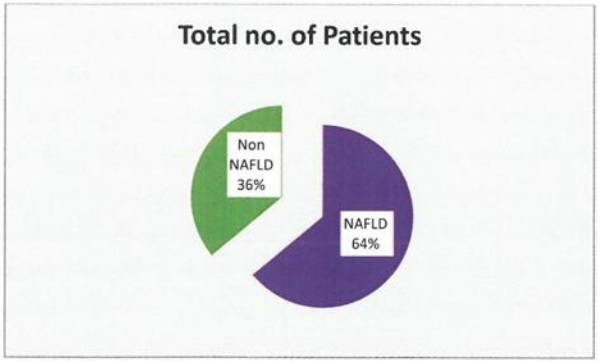

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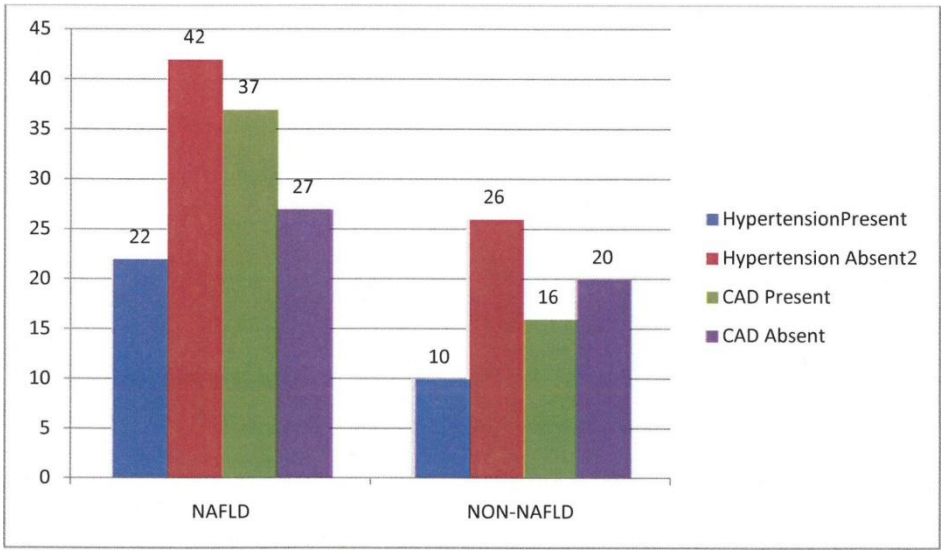
Figure 2: Correlation Of Nafld With Other Comorbid Conditions



Conclusion:

The results from this study have established a higher prevalence of NAFLD in type 2 DM population. So, a positive correlation between hyperinsulinemia, abnormal glucose tolerance and NAFLD. In our study, Prevalence of NAFLD higher in males as compare to female and highest in 50–59-year age group. NAFLD is associated with strong family history of type 2 DM, CAD, Metabolic Syndrome, Serum Triglyceride, and longer duration of DM. In our study elevated HBA1C level suggests that prevalence of NAFLD was higher in patients with uncontrolled DM. A Prevalence of NAFLD in our type 2 DM patients is high and increases with multiple components of metabolic syndrome. Among type 2 diabetes, NAFLD clusters with coronary risk factors. NAFLD is an increasingly important chronic liver disease next to alcoholic liver disease. Insulin resistance and oxidative stress play important roles in etio pathogenesis of non-alcoholic liver disease. NAFLD is usually asymptomatic and incidentally diagnosed on routine laboratory investigation. Liver biopsy remains the most sensitive and specific means of providing prognostic information but nowadays other non-invasive tests are upcoming and playing a major role in clinical practice. In the absence of definite therapies, treatment is generally directed at optimizing body weight and controlling risk factors. Liver transplantation is a therapeutic option for decompensated chronic liver disease.

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