Section: Surgery

Research

RELATION OF INSULIN RESISTANCE IN NON-ALCOHOLIC FATTY LIVER DISEASE

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Received : 06/09/2022
Received in revised form : 05/10/2022
Accepted : 17/10/2022

Keywords:
Non-alcoholic fatty liver disease, Insulin resistance, Fasting serum insulin.

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DOI: 10.47009/jamp.2022.4.5.5

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2022; 4 (5); 17-22

Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is a common hepatic disorder characterized by fat accumulation in the liver, identical to that seen in alcoholic fatty liver disease, but in patients who do not drink excessive amounts of alcohol (<20 gram/day). It is now considered to be the commonest problem in the western world affecting 15-40% of the general population and in Asian countries from 9-40%. NAFLD is strongly associated with both hepatic and adipose tissue insulin resistance as well as reduced whole-body insulin sensitivity. **Materials and Methods:** This was a hospital based observational and analytical study conducted among in the Department of General Medicine, M.K.C.G Medical College and Hospital, Berhampur. Total 50 cases of NAFLD and 50 control groups without NAFLD. All patients fulfilling inclusion criteria in which NAFLD is detected by means of USG performed for any reason will be considered as cases. Subjects will be considered as cases if they have fatty liver according to the standard criteria accepted by the American gastroenterology association i.e., an increase in hepatic echogenicity as a reference, the presence of enhancement and lack of differentiation in periportal intensity and the vascular wall due to great hyperechogenicity in the parenchyma. **Result:** Out of 50 cases, 46% patients had grade 1 fatty liver, 46 % had grade 2 with 4% patients presented with grade 3 fatty liver according to USG finding. Mean FBS was found to be significantly higher (P value 0.001) in NAFLD with insulin resistance patients (124.0±23.4) as compared to NAFLD without insulin resistance (96.3±10.6). Mean serum insulin was found to be significantly higher (P value 0.0001) in NAFLD with insulin resistance patients (13.6±3.5) as compared to NAFLD without insulin resistance (7.3±1.8). Serum bilirubin, ALT, AST was found to be not significant (p value>0.05) in NAFLD with insulin resistance (0.8±0.2mg/dl, 53.59±15.4IU/L, 40.2±10.9IU/L) as compared to NAFLD without insulin resistance (O.9±0.1mg/dl, 60.7±22.6IU/L, 46.4±16.4IU/L) respectively. **Conclusion:** This important statistical observation revealed that in insulin resistance patients there is continuous positive linear correlation with FBS, fasting serum insulin, serum TG, total cholesterol and LDL. Insulin resistance is found to be reliable indicator of severity of NAFLD. Our study revealed that there is a higher prevalence of insulin resistance in cases of NAFLD. Hence whenever NAFLD cases are encountered in clinical setting, all the patients must be evaluated for presence of insulin resistance which is calculated by HOMA-IR index.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common hepatic disorder characterized by fat accumulation in the liver, identical to that seen in alcoholic fatty liver disease, but in patients who do not drink excessive amounts of alcohol (<20 gram/day). It is now considered to be the commonest problem in the western world affecting 15-40% of the general population and in Asian countries from 9-40%.[1] The global obesity, TYPE 2 DM, has dramatically increased the prevalence of NAFLD and made it leading cause of chronic liver disease. NAFLD is considered the hepatic manifestation of metabolic syndrome and shares a strong association with type 2 DM, obstructive sleep apnoea, cardio vascular disease. NAFLD specifically NASH is often associated with DM with

ISSN (O): 2687-5365; ISSN (P): 2753-6556

associated 60 to 76% prevalence rate of NAFLD and 22% prevalence rate of NASH.[2]

NAFLD is strongly associated with both hepatic and adipose tissue insulin resistance4-6 as well as reduced whole-body insulin sensitivity.[3] Excess intraabdominal fat in particular may be a key determinant in the pathogenesis of NAFLD, via both its strong association with insulin resistance and possibly as a source of FFAs. Intraabdominal fat accumulation is well recognized to be associated with insulin resistance and central adiposity, so that, even in lean individuals, the accumulation of fat in this depot is associated with reduced insulin sensitivity.[4]

Patient with NAFLD have increased level of serum free fatty acid as compared to patient without NAFLD, attributed to a failure of insulin-mediated suppression of lipolysis, allowing release of excess FFA in bloodstream.[5,6]

The pathologic picture of NAFLD, ranging from simple steatosis to steatohepatitis, advanced fibrosis, cirrhosis occurs in patients who don't consume alcohol, which resembles that caused by alcoholic liver disease. Nonalcoholic steatohepatitis is characterized by hepatic steatosis, injury to hepatic cells, hepatic inflammation, fibrosis and necrosis, which is considered as intermediate stage of NAFLD.[7] Fatty liver disease is believed to be the hepatic consequence of metabolic syndrome or a cluster of metabolic disorders.

Insulin resistance is defined as resistance to metabolic effects of insulin including suppressive effects of insulin on endogenous glucose production, stimulatory effect of insulin on peripheral glucose uptake, glycogen synthesis and also inhibitory effect of insulin on adipose tissue. Insulin resistance is associated with DM, hypertension, raised VLDL cholesterol, triglyceride and low plasma HDL cholesterol.[8]

Insulin resistance from excessive accumulation of FFA is thought to be a primary factor in the development of steatosis in most patients with NAFLD. Impairment of insulin signalling in adipose tissue and the liver, along with increased dietary fat and de novo lipogenesis, contributes to hepatic steatosis in NAFLD.[9] As Incidence of NAFLD is increasing worldwide and It has become the most common cause of Chronic Liver Disease. Finding the causes of NAFLD is utmost important. So in this Study Correlation of Insulin Resistance with NAFLD, Lipid Profile In NAFLD, Ferritin and other markers Association with NAFLD will be assessed.

MATERIALS AND METHODS

This was an hospital based observational and analytical study conducted among in the Department of General Medicine, M.K.C.G Medical College and Hospital, Berhampur. Total 50 cases of NAFLD and 50 control groups without NAFLD.

Inclusion Criteria

- All patients diagnosed as NAFLD by USG.
- Age>18 years for both males and females.

Exclusion Criteria

- Patients<18 years and >85 years.
- Patient with history of jaundice and Australia Ag positive
- Patient with history of alcohol intake.
- Patient with history of drug intake such as steroids, heparin, CCB, amiodarone, valproic acid, antiviral agent and estrogen.

All patients fulfilling inclusion criteria in which NAFLD is detected by means of USG performed for any reason will be considered as cases.

Subjects will be considered as cases if they have fatty liver according to the standard criteria accepted by the American gastroenterology association i.e., An increase in hepatic echogenicity as a reference, the presence of enhancement and lack of differentiation in periportal intensity and the vascular wall due to great hyperechogenicity in the parenchyma.

Insulin resistance assessed by Homeostasis model assessment-insulin resistance (HOMA_IR INDEX)

HOMA_IR= FASTING SERUM INSULIN* FASTING PLASMA GLUCOSE/ 405 (glucose in mg/dl and insulin in μIU/ml) In adults, HOMA_IR>2.5 suggest insulin resistance.

Ultrasonographic Examination

Diagnosis and grading of liver steatosis was done by using USG by two radiologists who did not have information about the patients. Hepatic sonography was done following 8h fasting using a 3.5 MHz probe. Both supine and right anterior oblique views were obtained. Holding inspiration temporarily enabled visualization of the dome of liver. Subjects will be considered cases if they have fatty liver according to the standard criteria accepted by the American gastroenterology association i.e, An increase in hepatic echogenicity as a reference, the presence of enhancement and lack of differentiation in the periportal intensity and the vascular wall due to great hyperechogenicity in the parenchyma. NAFLD cases are graded as per Gore et al.[10]

Grade 1- normal visualization of diaphragm/intrahepatic vessels

Grade 2- impaired visalization of diaphragm/intrahepatic vessels

Grade 3- poor visalization of diaphragm/intrahepatic vessels

Control

Age, sex, ethnic matched adults WERE in this study as controls. All the controls were without NAFLD.

Statistical Analysis

Data was analyzed using the SPSS software, version 21.0. Descriptive results are expressed as mean and SD of various parameters in study group and

ISSN (O): 2687-5365; ISSN (P): 2753-6556

qualitative data was presented as frequency and percentage. Statistical significance was determined by using Fisher's exact test, and Pearson's chi-squared test and P value. P value <0.05 was considered as statistically significant. Regression analyses were done to find out association of HOMA_IR level to other parameters like FBS, serum insulin, serum triglyceride, total cholesterol, HDL, LDL, VLDL.

RESULTS

Out of 50 cases,46% patients had grade 1 fatty liver,46 % had grade 2 with 4% patients presented with grade 3 fatty liver according to USG finding.

Table 1: Distribution of grades of fatty liver based on USG findings

USG Grading of Fatty Liver	No. Of Patients	Percentage
GRADE 1	23	46
GRADE 2	23	46
GRADE 3	4	8

Table 2: Age distribution of NAFLD patients

Age group(years)		Fatty liver grading			Total	Percentage
		1	2	3		
	20-29	6	2	0	8	16
	30-39	3	4	0	7	14
	40-49	4	5	2	11	22
	50-59	9	7	2	18	36
	>60	1	5	0	6	12
Total		23	23	4	50	100

In this study group the mean age of NAFLD patient was 46.50±12.45 years with minimum age 21 to maximum of 65 years. The majority of patients were in age group 50-59 years (36%) followed by 40-49 years(22%).

Table 3: Gender distribution of NAFLD patients

Sex		Fatty liver grading			Total	Percentage
		1	2	3		
	F	12	7	1	20	40
	M	11	16	3	30	60
Total		23	23	4	50	100

In the NAFLD patients majority are male i.e 60%(30) while females constituted 40%(20) of total patient load with male to female ratio 3:2.

Table 4: Comparison between Glycemic Status between NAFLD with and without Insulin Resistance

Variables	NAFLD Without Insulin Resistance (HOMA-IR<2.5) (Mean±SD)	NAFLD With Insulin Resistance(HOMA-IR>2.5)(Mean±SD)	P Value
FBS	96.38±10.66	124.0±23.48	0.0001
SERUM INSULIN(μIU/ml)	7.3±1.83	13.6±3.5	0.0001

Mean FBS was found to be significantly higher (P value 0.001) in NAFLD with insulin resistance patients (124.0±23.4) as compared to NAFLD without insulin resistance (96.3±10.6).
Mean serum insulin was found to be significantly higher (P value 0.0001) in NAFLD with insulin resistance patients (13.6±3.5) as compared to NAFLD without insulin resistance (7.3±1.8).

Table 5: Comparison of LFT between NAFLD with and without Insulin Resistance

VARIABLES	NAFLD WITHOUT INSULIN RESISTANCE(HOMA-IR<2.5) (MEAN±SD)	NAFLD WITH INSULIN RESISTANCE(HOMA-IR>2.5)(MEAN±SD)	P VALUE
SERUM BILLIRUBIN(mg/dl)	0.92±0.13	0.83±0.26	0.154
ALT(IU/L)	60.7±22.6	53.59±15.42	0.192
AST(IU/L)	46.43±16.45	40.24±10.95	0.117

Serum bilirubin, ALT, AST was found to be not significant (p value>0.05) in NAFLD with insulin resistance (0.8±0.2mg/dl, 53.59±15.4IU/L, 40.2±10.9IU/L) as compared to NAFLD without insulin resistance (O.9±0.1mg/dl, 60.7±22.6IU/L, 46.4±16.4IU/L) respectively.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 6: Comparison of Variables of Lipid Profile between NAFLD with and without Insulin Resistance

Variables	NAFLD without insulin resistance (HOMA-IR<2.5) (mean±SD)	NAFLD with INSULIN resistance (HOMA-IR>2.5) (Mean±SD)	P value
Total Cholesterol (mg/dl)	164.19±11.9	195.0±23.6	0.0001
Triglyceride (mg/dl)	134.8±15.03	220.24±53.91	0.0001
HDL (mg/dl)	42.38±8.4	35.83±6.15	0.003
LDL (mg/dl)	95.7±10.80	117.0±17.86	0.0001

Mean cholesterol was found to be significantly higher (p value 0.0001) in NAFLD with insulin resistance patients (195.0±23.6 mg/dl) as compared to NAFLD without insulin resistance (164.1±12.1mg/dl). Mean serum triglyceride was found to be significantly higher (p value 0.0001) in NAFLD with insulin resistance patients (220.2±53.9 mg/dl) as compared to NAFLD without insulin resistance (134.8±15.03mg/dl). Mean serum HDL was found to be significantly lower (p value 0.003) in NAFLD with insulin resistance patients (35.8±6.1 mg/dl) as compared to NAFLD without insulin resistance (42.3±8.4mg/dl). Mean serum LDL was found to be significantly higher (p value 0.0001) in NAFLD with insulin resistance patients (117.0±17.8 mg/dl) as compared to NAFLD without insulin resistance (95.7±10.8mg/dl).

Table 7: Comparison of Anthropometric and Biochemical Parameters in Cases (With NAFLD) and Controls (Without NAFLD)

VARIABLES	CASES(MEAN±SD)	CONTROLS(MEAN±SD)	P VALUE
Age (years)	46.5±12.4	46.4±12.3	
BMI (kg/m2)	24.8±3.1	22.6±1.4	
WAIST circumference (cms)	88.8±3.9	83.1±5.6	
HIP circumference (cms)	86.4±3.3	81.04±5.2	
WHR	1.02±0.01	1.02±0.01	
SBP (mm/hg)	128.6±9.8	129.08±9.9	
DBP (mm/hg)	82.9±7.9	82.8±6.6	
FBS (mg/dl)	112.4±23.4	85.08±7.4	
Sr Billirubin (mg/dl)	0.87±0.2	0.91±0.19	
ALT (IU/L)	56.5±18.9	32.3±3.7	
AST (IU/L)	42.8±13.7	30.1±3.6	
Total Cholesterol (mg/dl)	182.06±24.8	173.4±16.3	
Triglyceride (mg/dl)	184.4±59.7	131.6±15.7	
HDL (mg/dl)	38.5±7.8	48.8±6.7	
LDL (mg/dl)	108.06±18.5	94.6±14.3	
Serum Insulin (µIU/ml)	10.9±4.2	8.8±2.2	
HOMA-IR	3.2±1.7	1.8±0.5	

DISCUSSION

In our study out of 50 cases of NAFLD, 23(46%) patients had grade 1 fatty liver, 23(46%) patients had grad 2 fatty liver and 4(8%) patients had grade 3 fatty liver. Similar study performed by Roli Agarwal 10 who observed 48.1%, 40.3%, 11.3% had grade 1,2,3 fatty liver respectively, which is comparable to our present study.

Insulin resistance is the most important mechanism in pathogenesis of NAFLD and is a major risk factor for progression to severe liver disease. 19 (38%) out 50 patients were diabetic with 6 (12%) patients had impaired glucose tolerance which can be compared with studies done by Bacon et al,[11] but higher prevalence is seen in study done by Deepa uchil et al.[12] All the patients of grade 3 were diabetic i.e. 4 (100%). Majority of patients (14) of grade 2 were diabetic with 2 had impaired glucose tolerance. The relation between blood sugar with increasing grades of fatty liver is highly significant (p value.0001).[13] Another study done by Deepa uchil et al where mean observed was higher than current study i.e. 126.6±45.83. Mean fasting blood sugars in grade 1 was found to be 96.8±11.79, 123.35±23.58 in grade 2 and 139.0±13.49 in grade 3.

Mean serum bilirubin in our study was found to be 0.87±0.22 mg/dl. Elevated bilirubin levels were reported in 8% by Agarwal et al and 7.69% by Amrapurkar et al which is contrasted to our study. But most of the western studies have reported normal bilirubin levels in NAFLD patients.[14,15]

Elevation of serum transaminase was the most common biochemical abnormality in our patients. ALT and AST levels were elevated in 44(88%) and 36(72%) of our patients respectively. Similar study was done by Agarwal et al who reported elevated ALT and AST in 97.6% and 98.4% of patients respectively.[16] But we didn't find any statistical significant association between increasing grades of NAFLD with ALT (P value 0.637) and AST (P value 0.938).

In our study, all the patients had ALT/AST ratio >1 which is similar to study done by Amarpurkar et al whereas Agarwal et al observed the same in 92% of patients.[17,18]

Asian Indians are more prone to develop atherogenic dyslipidemia i.e. combination of hypertriglyceridemia, low level of HDL cholesterol and high level of LDL cholesterol. In our study, we also observed a strong association between NAFLD and dyslipidemia.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

In current study mean total cholesterol was 182.06± 24.79 mg/dl and 12(24%) of total patients had increased serum cholesterol levels. So, the association between increasing grades of NAFLD with total cholesterol was highly significant with p value 0.001. Similar study was done Roli Agarwal et al who also reported 50-80% of patients had hypercholesterolemia with mean total cholesterol 201.37±44.49 mg/dl.[10]

In present study mean serum triglyceride was 184.36± 59.72 mg/dl.26(52%) patients in our study had hypertriglyceridemia which is comparable to above mentioned studies and showed statistical significance with increasing grades of fatty liver (p value 0.0001).

In this present study mean HDL was 38.58±7.8mg/dl. 37(74%) patients had low HDL but relation between serum HDL with increasing grades of fatty liver is not statistically significant (p value 0.999). Mean HDL levels in grade 1 was 40.3±8.38mg/dl, in grade 2-37.65±7.11mg/dl and in grade 3 was 34.0±7.61mg/dl.17(45.94%) patients with grade 1 fatty liver,17(45.94%) with grade 2 fatty liver, 3 (8.10%) with grade 3 fatty liver had low HDL levels. Other studies have reported a prevalence of 28.2% to 66%.

In current study mean serum LDL was 108.06±18.51mg/dl and 9(18%) of total patient had increased serum LDL levels which showed statistically significant relation with increasing grades of fatty liver with p value 0.001. Roli Agarwal et al reported elevated LDL in 25% of patients with a mean of 115±35.49mg/dl.[10]

Mean fasting serum insulin in this study was 10.97±4.28 µU/ml. Mean serum insulin levels in grade 1 was 8.5±3.3 µU/ml, in grade 2 was 12.89±4.19 µU/ml and in grade 3 was 13.64±3.25 µU/ml. In the current study mean HOMA-IR was 3.2±1.7 and 29(58%) of NAFLD patients showed HOMA-IR index more than 2.5 suggestive of insulin resistance. The prevalence of IR is our study is lower than the above-mentioned studies.

Mean HOMA-IR index in grade 1 was 2.04±0.7, in grade 2 was 4.2 ±1.6 and grade 3 was 4.7±1.5. This observation is compatible with current knowledge of β cells (Das et al 2008). 18 ID Bookman et al (1999) suggested that insulin resistance correlates with increasing severity of liver histology from healthy controls to fatty liver and NASH.[19]

In this study, out of 23 patients of grade 1, 17(73.91%) patients had no insulin resistance and 6(26.09%) patients had insulin resistance. In grade 2, 19(82.60%) patients and in grade 3, 4(100%) patients had insulin resistance. The mean value of HOMA-IR was 3.28±1.72 which was more than 2.5 suggestive of insulin resistance. There was a statistical significance (p value-0.0001) between HOMA-IR index with increasing grades of fatty liver.

We have found 29 cases of NAFLD had insulin resistance with HOMA IR>2.5 whereas in control without NAFLD had only 3 cases with IR. 23(79.31%) were males in NAFLD patients with IR and 6(20.68%) were females. Mean Age was found to be significantly higher in NAFLD with insulin resistance patients (48.72±10.83 years) as compared to NAFLD without insulin resistance (43.43±14.10 years).

Mean FBS was found to be significantly higher (p value 0.0001) in NAFLD with insulin resistance patients (124.0±23.4) as compared to NAFLD without insulin resistance (96.3±10.6). Mean serum insulin was found to be significantly higher (p value 0.0001) in NAFLD with insulin resistance patients (13.6±3.5) as compared to NAFLD without insulin resistance (7.3±1.8).

Serum bilirubin, ALT, AST was found to be not significant (p value) in NAFLD with insulin resistance(0.8±0.2mg/dl,53.59±15.4IU/L,40.2±10.9IU/L) as compared to NAFLD without insulin resistance (O.9±0.1mg/dl, 60.7±22.6IU/L, 46.4±16.4IU/L).

Mean cholesterol was found to be significantly higher (p value 0.0001) in NAFLD with insulin resistance patients (195.0±23.6 mg/dl) as compared to NAFLD without insulin resistance (164.1±12.1mg/dl). Mean serum triglyceride was found to be significantly higher (p value 0.0001) in NAFLD with insulin resistance patients (220.2±53.9 mg/dl) as compared to NAFLD without insulin resistance (134.8±15.03mg/dl). Mean serum HDL was found to be significantly lower (p value 0.003) in NAFLD with insulin resistance patients (35.8±6.1 mg/dl) as compared to NAFLD without insulin resistance (42.3±8.4mg/dl). Mean serum LDL was found to be significantly higher (p value 0.0001) in NAFLD with insulin resistance patients (117.0±17.8 mg/dl) as compared to NAFLD without insulin resistance (95.7±10.8mg/dl).[20]

CONCLUSION

This important statistical observation revealed that in insulin resistance patients there is continuous positive linear correlation with FBS, fasting serum insulin, serum TG, total cholesterol and LDL. Insulin resistance is found to be reliable indicator of severity of NAFLD.

Our study revealed that there is a higher prevalence of insulin resistance in cases of NAFLD. Hence whenever NAFLD cases are encountered in clinical setting, all the patients must be evaluated for presence of insulin resistance which is calculated by HOMA-IR index.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556