Significance of Diabetes Mellitus in the Risk Factor Analysis of Non Alcoholic Steatohepatitis and Cardiovascular Disease

[1] Dr. C. Subramanian, [2] Dr.Prasanth.C.B &`[3] Ramya. M. S.

[1] Associate Professor, Department of Statistics, Annamalai University, manistat@yahoo.co.in .

[2]Assistant Professor,Department of Statistics, Sree Keralawarma College, Kerala, cbpwarrier@gmail.com

[3] Research Scholar, Department of Statistics, Annamalai University, msramyaotp@gmail.com

Abstract. Non-alcoholic steatohepatitis (NASH) is commonly associated with type 2 Diabetes Mellitus (DM). Prevalence of NASH in type 2 DM has not been well studied and there is an epidemic rise in type 2 DM in developed and developing countries. Its association with chronic liver disease in the form of NASH makes it an important health problem. The world wide prevalence of non alcoholic fatty liver disease (FLD) is estimated to have more in adults. Non Alcoholic Fatty Liver Disease (NAFLD) is often associated with insulin resistance and is strongly associated with type 2 diabetes mellitus and obesity. NAFLD patients are at risk of progressing to NASH and ultimately cirrhosis; they are also at higher risk of cardiovascular diseases (CVD), including coronary heart disease and stroke. In this paper we are trying to analyse the risk of new CVD event in child-bearing women with diabetic and non diabetic issues. Baseline characteristics were age, obesity, diabetic level, hypertension, cholesterol level etc. and our attempt is to derive a statistical model for estimating the association of many such components with blood sugar. Finally the significance of the model is statistically tested. We also propose to expand our study to prove whether NASH is an independent risk factor for CVD later.

Keywords: statistical Significance, Diabetes Mellitus, Non Alcoholic Fatty Liver Disease, cirrhosis.

I. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a condition in which excess fat is stored in your liver. This build-up of fat is not caused by heavy alcohol use. When heavy alcohol use causes fat to build up in the liver, this condition is called alcoholic liver disease. Two types of NAFLD are simple fatty liver and non-alcoholic steatohepatitis (NASH). Simple fatty liver and NASH are two separate conditions. People typically develop one type of NAFLD or the other, although sometimes people with one form are later diagnosed with the other form of NAFLD. Simple fatty liver, also called non-alcoholic fatty liver (NAFL), is a form of NAFLD in which you have fat in your liver but little or no inflammation or liver cell damage. Simple fatty liver typically does not progress to cause liver damage or complications. NASH is a form of NAFLD in which you have hepatitis inflammation of the liver—and liver cell damage, in addition to fat in your liver. Inflammation and liver cell damage can cause fibrosis, or scarring, of the liver. NASH may lead to cirrhosis or liver cancer. Experts are not sure why some people with NAFLD have NASH while others have simple fatty liver.

Baseline information was obtained *via* a questionnaire on general information, physical examination (height, weight, and blood pressure), laboratory tests (triglycerides, total cholesterol, blood glucose, aspartate aminotransferase (AST) or serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT) or Serum glutamic pyruvic transaminase (SGPT)), Body Mass Index (BMI) and Waist Circumference **(**WC). Prevalence of NAFLD and NASH in our study of type 2DM patients is high and increases with multiple components of metabolic

syndrome. (Metabolic syndrome is a cluster of conditions that occur together, increasing your risk of heart disease, stroke and type 2 diabetes. These conditions include increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels). BMI is obtained by dividing body weight in kilograms by height in meters squared. In developed countries, subjects with a BMI $\geq$ 25 kg/m^2 are defined as overweight and those with a BMI $\geq$ 30 kg/m^2 are defined as obese, and there are good associations and positive predictive effects between BMI and obesity-related chronic diseases. Both obesity and NAFLD are closely related to T2DM. Heredity is not a factor for NASH. As DM is attained by heredity, there is no chance for NAFLD. It is a life style disease. TG level increase means there is a high risk of CVD. As SGPT and SGOT levels are normal levels in most data, there exist chances of fatty liver.

NAFLD is more common in people who have certain conditions, including obesity and conditions that may be related to obesity, such as type 2 diabetes. Researchers have found NAFLD in 40 to 80 percent of people who have type 2 diabetes and in 30 to 90 percent of people who are obese. In research that tested for NAFLD in people who were severely obese and undergoing bariatric surgery, more than 90 percent of the people studied had NAFLD. The majority of people with NAFLD have simple fatty liver, and people with simple fatty liver typically don't develop complications. NASH can lead to complications, such as cirrhosis and liver cancer. People with NASH have an increased chance of dying from liver-related causes. If NASH leads to cirrhosis, and cirrhosis leads to liver failure, you may need a liver transplant to survive.

Cardiovascular disease (CVD), is a general term for a disease of the heart or blood vessels. Blood flow to the heart, brain or body is reduced because of a blood clot (thrombosis) or a build-up of fatty deposits inside an artery, leading to hardening and narrowing of the artery (atherosclerosis). The three main types of CVD are coronary heart disease, stroke & peripheral arterial disease. Coronary heart disease occurs when your heart's blood supply is blocked or interrupted by a build-up of fatty substances (called atheroma) in the coronary arteries. The coronary arteries are two major blood vessels that supply the heart with blood. Stroke is a serious medical condition that occurs when the blood supply to the brain is disturbed. Peripheral arterial disease is also known as peripheral vascular disease. It occurs when there is a blockage in the arteries to your limbs (usually your legs).

2. Review of Literature

Prasanth et.al., (2017) conducted a study on "Prevalence of NAFLD in Patients with Type 2 Diabetes Mellitus" and concluded that prevalence of NAFLD and NASH in our cohort of type 2 DM patients is high and increases with multiple components of metabolic syndrome. NASH and advanced fibrosis can occur in diabetic patients without any symptoms, signs or routine laboratory test abnormalities. Wenjie Dai et.al.,(2017) studied "Prevalence of Nonalcoholic Fatty Liver Disease in Patients with Type2 Diabetes Mellitus" and concluded that the high pooled prevalence of NAFLD in T2DM patients found in this study significantly underscores the need for early assessment of NAFLD and the importance of strengthening the management of NAFLD in T2DM patients.

Nasrin Amiri et.al., (2017) conducted the study, "Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis." The findings indicated that the overall prevalence of NAFLD among type 2 diabetes mellitus patients is significantly higher. It can be concluded that type 2 diabetes mellitus patients should be managed to prevent NAFLD. Alessandro Mantovani et.al., (2018) studied "Non-Alcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis" and found that NAFLD is significantly associated with a twofold increased risk of incident diabetes. However, the observational design of the eligible studies does not allow for proving causality.

Shunquan Wu et.al., (2016) conducted a study "Association of Non-alcoholic Fatty Liver Disease with Major Adverse Cardiovascular Events: A Systematic Review and Meta-analysis." The main results of meta-analysis are the following: (1) NAFLD was not associated with overall mortality and CVD mortality; (2) NAFLD was associated with an increased prevalence and/or incidence of other adverse cardiovascular events, including CVD, CAD, hypertension, and atherosclerosis; (3) NASH was not associated with overall mortality and CVD mortality but was associated with an increased incidence of CVD. These results are important given the high prevalence of NAFLD in the general population and the concerns raised by the adverse metabolic profile are associated with this disease and NASH.

Hagstrom et.al., (2019) studied "Cardiovascular Risk Factors in Non-alcoholic Fatty Liver Disease." The study concluded that patients with NAFLD are at an increased risk for CVD compared to matched controls, but histological parameters do not seem to independently predict this risk. Carrie et.al.,(2018) conducted a study on "The Association between Non-alcoholic Fatty Liver Disease and Cardiovascular Disease Outcomes and found that the causal relationship of CVD and NAFLD remains under investigation, but the strong bidirectional association between CVD and NAFLD warrants clinical intervention in patients with NAFLD to modify metabolic risk factors, including T2DM, dyslipidemia, hypertension, and obesity.

Mathews et.al.,(2018) conducted a study on "Non-alcoholic Steatohepatitis, Obesity, and Cardiac Dysfunction." It summarises obesity as a major factor in the development of Nonalcoholic Fatty Liver Disease (NAFLD) and its progression to steatohepatitis. Patients with NAFLD have a significant increase in cardiovascular disease risk. For biopsy-proven NASH, Vitamin E and Pioglitazone are the recommended medical treatments in addition to lifestyle modification. Rashmee and Gagan (2017) studied "Non-alcoholic Fatty Liver Disease and Cardiovascular Risk and concluded that Non-alcoholic Fatty Liver Disease (NAFLD) is often associated with insulin resistance and is strongly associated with type 2 diabetes mellitus and obesity. NAFLD is now recognized as a risk factor for poor cardiovascular outcomes including mortality and morbidity from major vascular events. As a whole, NAFLD patients may benefit from more careful surveillance and early treatment interventions.

Dharmalingam M, Yamasandhi P G (2018) conducted a study on "Alcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus" and concluded that T2DM and NAFLD have a common association. The increasing prevalence makes it a public health problem. Targher G et. al., (2007) conducted study on "Non-alcoholic Fatty Liver Disease is Independently Associated with an Increased Incidence of Cardiovascular Events in Type 2 Diabetic Patients." The findings suggest that NAFLD is associated with an increased incidence of CVD in type 2 diabetic patients, independent of traditional CVD risk factors and metabolic syndrome components.

Bhatt KN et.al., (2017) conducted study 0n "Prevalence of Nonalcoholic Fatty Liver Disease in Type 2 Diabetes Mellitus and its Relation with Insulin Resistance in South Gujarat Region." The study revealed a high incidence of NAFLD in Type 2 diabetes patients stressing the need for early screening. Claudio Tana et.al., (2019) conducted study on "Cardiovascular Risk in Non-Alcoholic Fatty Liver Disease: Mechanisms and Therapeutic Implications" to conclude that all cardio-metabolic risk factors should be carefully and routinely screened among patients with NAFLD, and that disease management should be focused on both specific lifestyle modifications and aggressive risk factors modification, which would not only reduce the risk of liver disease progression, but may also provide benefits by reducing the risk of developing cardiac complications.

Jonathan M. Hazlehurst, et.al., (2016) studied "Non-alcoholic Fatty Liver Disease and Diabetes and concluded that diabetes and NAFLD are reciprocal risk factors and when they occur together, an increasing body of data demonstrates that diabetes is more difficult to manage and that NAFLD is more likely to progress. Giovanni Targher, et.al., (2005) conducted study on "Nonalcoholic Fatty Liver Disease and Risk of Future Cardiovascular Events Among Type 2 Diabetic Patients" and suggested that the metabolic syndrome predicts incidents of cardiovascular disease (CVD), so it is possible to hypothesize that NAFLD patients might portend a greater CVD risk and that NAFLD itself might confer a CVD risk above that associated with individual metabolic syndrome risk factors.

Dyson JK, et.al., (2014) studied "Non-alcoholic Fatty Liver Disease: A Practical Approach to Treatment" concluded that lifestyle interventions aimed at weight loss and increased activity are essential for all patients with NAFLD and if sustained are effective in the treatment of NAFLD. Carrie R. Wong, et. Al., (2018) conducted study on "The Association between Non-alcoholic Fatty Liver Disease and Cardiovascular Disease Outcomes" and concluded that the causal relationship of CVD and NAFLD remains under investigation, but the strong bidirectional association between CVD and NAFLD warrants clinical intervention in patients with NAFLD to modify metabolic risk factors, including T2DM, dyslipidemia, hypertension, and obesity.

3. **Methodology and Data Analysis**

The proposed research is to develop a statistical model which specifies the significance of diabetes mellitus in the risk factor analysis of NASH and CVD. From the literatures we can see that there are some relations between diabetes mellitus, NASH and CVD. Here, in the initial stage of the research work, a regression model is formulated to show the effect of age, weight, waist circumference etc. on blood sugar. We also discussed the various risk factors which causes NAFLD and CVD. 375 child bearing diabetic women were screened from various hospitals in the 2 districts ---Palakkad and Malappuram--- at Kerala to make a real data analysis.135 (36%) of them were with diabetics as a hereditary component. 219 of them were reported with fatty liver. That is 59% of carrying ladies were with FLD. The analysis of DM with related components will be more effective for further future analysis. Age, height, weight, waist circumference, the presence of comorbidities (diabetes, arterial hypertension), SGOT, SGPT, total cholesterol, Triglycerides (TG) and Body Mass Index (BMI) were evaluated. Using the real values of above factors a frequency table is formulated and a bar diagram is drawn based on the table. The level of association is shown through a dendrogram. A regression model is obtained to predict the effect of various baseline characteristics with CVD and NAFLD on blood sugar. Based on the abdominal ultra sound scanning images, fatty liver is

confirmed. Blood sugar, SGOT, SGPT, total cholesterol, Triglycerides (TG) etc was obtained from bio–chemistry reports. Some of the patients having control level of SGPT, SGOT have symptoms of fatty liver shown in their Ultra Sound Scanning. Central obesity as measured by weight circumferences (WC) and SGPT levels were significantly higher in people with fatty liver.

Table 1- Frequency Table: Age of People

Age	Frequency
15-20	3
20-25	18
25-30	126
30-35	129
35-40	69
40-45	27
45-50	3
total	375

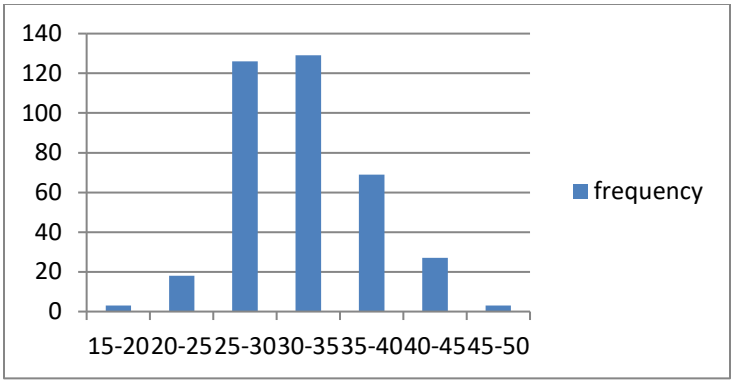

Figure 1-Bar Chart Age: Frequency

From the bar chart we analysed that the child bearing women have more number of type2 diabetic patients in the age 30 - 35.

Table 2-Correlation Coefficient between the Components

Risk Factor	Correlation Coefficient
Weight & Waist Circumference	0.69
Waist Circumference & TG	0.588
SGOT& TG	0.709
SGPT& BMI	0.597
Weight & BMI	0 .87
Waist Circumference & BMI	0.597
SGPT & TG	0.693
Systolic Pressure & Diastolic Pressure	0.876

Table 2 shows the correlation between the different base line characteristics of study. Correlation Coefficient greater than 0.5 is indicative of the high risk of having NAFLD and CVD. High positive correlation indicates that it is a risk factor for NAFLD. The correlation between SGPT, SGOT and TG indicates an increasing level of SGPT, SGOT enzymes that affect the functioning of liver and causes liver damage. As TG level increases there is a high risk of CVD. The high correlation of hypertension also indicates that high risk of CVD.

Dendrogram. The dendrogram is a multilevel hierarchy where clusters at one level are joined together to form the clusters at the next levels. This makes it possible to decide the level at which to cut the tree for generating suitable groups of data objects. It is a type of tree diagram showing hierarchical clustering — relationships between similar

sets of data. They are frequently used in biology to show clustering between genes or samples, but they can represent any type of grouped data. The dendrogram is a visual representation of the compound correlation data. The individual compounds are arranged along the bottom of the dendrogram and are referred to as leaf nodes. Compound clusters are formed by joining individual compounds or existing compound clusters with the join point referred to as a node.

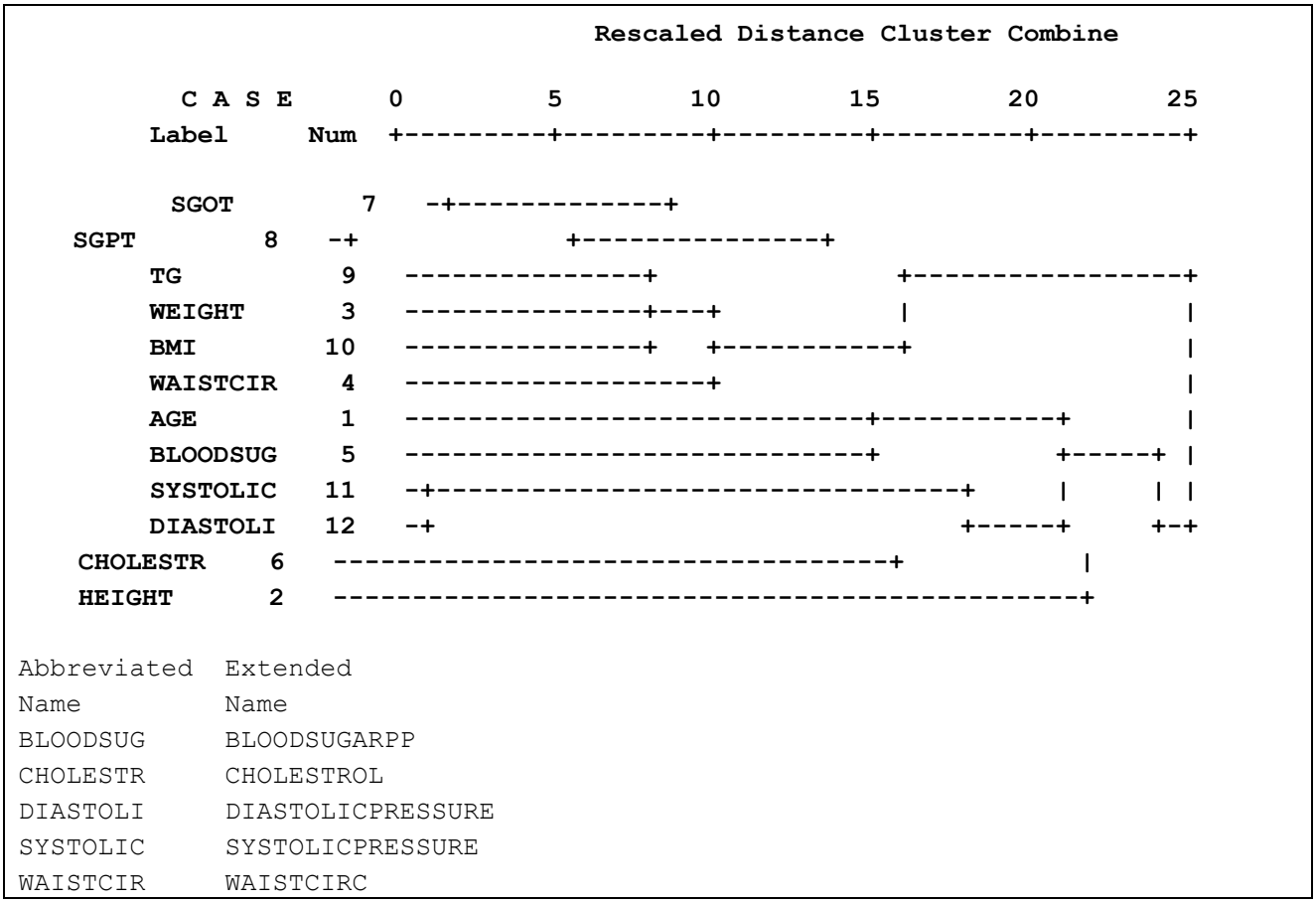

Figure 2-Dendrogram using Average Linkage (Between Groups)

Figure 2 indicates the dendrogram of the average linkage data variables. In the dendrogram it is found that the labels SGOT and SGPT with label numbers 7 and 8 has first level of association with the risk of NAFD if their values are between 0-5. SGOT and SGPT affect the predicted variable in the same way. That means, these two components are equally affected in the predicted variable NAFLD. The labels systolic and diastolic pressure with label numbers 11 and 12 also has first level of association. Therefore there exists a high correlation between these risk factors and CVD. The labels SGPT, SGOT, with label numbers 7 and 8 have second level of association if their values are between 5-10. TG, Weight, BMI with label numbers 9, 3 and 10 will also have second level of association. There is also a positive correlation. That is, these variables affect directly in predicted variables, NAFLD and CVD. Also the labels Weight, BMI and Waist CIR with label numbers 3, 10 and 4 have third level of association. That means these three variables also affect the predicted variables.

Regression Analysis. Regression, in statistics, is a process for determining a line or curve that best represents the general trend of a data set. Linear regression results in a line of best fit, for which the sum of the squares of the vertical distances between the proposed line and the points of the data set are minimized. Co-linearity, in statistics, gives the correlation between predictor variables (or independent variables), such that they express a linear relationship in a regression model. When predictor variables in the same regression model are correlated, they cannot independently predict the value of the dependent variable. In other words, they explain some of the same variance in the dependent variable, which in turn reduces their statistical significance. The variance inflation factor (VIF) is most widely-used diagnostic for multi co-linearity. It is called the variance inflation factor because it estimates how much the variance of a coefficient is "inflated" because of linear dependence with other predictors.

Table 3- Anova

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	29930.36	9	3325.597	4.300	0.008
	Residual	13149.007	17	773.471		
	Total	43079.369	26			

So a good regression model is there with: **a.** Predictors: Constant(C), Age(A), Height(H), Weight (W), Waist Circ(WC), Cholestrol(CH), SGOT(SO), SGPT(SG), BMI(BM), Systolic Pressure(SP), & Diastolic Pressure(DP)
b. Dependent Variable: Bloodsugar (Y)

Table 4-Regression

Model Summary			
R	R Square	Std. Error of the Estimate	Durbin-Watson
0.78	0. 61	15.811	1.69

Durbin-Watson 1.69 is an acceptable one for the model.

Table 5- Regression Analysis: Coefficients

	Coefficients	Collinearity Statistics VIF (all < 10)
(Constant)	191.703	
Age	3.155	1.779
Weight	-2.340	2.348
Waist Circ	4.914	2.672
Cholestrol	0.139	2.006
SGOT	2.111	7.243
SGPT	1.784	8.993
BMI	-5.697	4.283
Systolic Pressure	0.991	5.184
Diastolic Pressure	-1.568	5.216

Here all VIF are < 10 and implies no multi co-linearity.

So BLOODSUGAR

(BP) = 191.7 + 191.7A+3.15H -2.3W + 4.9 WC + 0.12CH + 2.1SO + 1.8SG - 5.7BM 0.9 SP – 1.6 DP

The regression model is:

$$\mathbf{Y = 191.7 + 3.15\ X_1 - 2.3\ X_2 + 4.9\ X_3 + 0.12\ X_4 + 2.1\ X_5 + 1.8\ X_6 + - 5.7\ X_7 + 0.9\ X_8 - 1.6\ X_9 + e}$$

where **e** is almost Standard Normal e ~ N (0, 1).

The above analysis clearly reveals that the regression model fits well.

4. CONCLUSION. We have so far discussed the risk of new CVD and NASH event in child bearing women with diabetic and non diabetic. Out of 375 child bearing diabetic women, 135 (36%) of them are with diabetics as a hereditary component. 219 of them were reported with fatty liver. That is 59% of carrying ladies were with FLD. A regression analysis is conducted on the observations taken from child bearing women having diabetics to evaluate the effect of the various risk factors of NASH and CVD on blood sugar and a statistical model is derived**.** From the analysis the relation between predictor variables such as age, weight, waist circumference etc with the dependent variable blood sugar is expressed as a linear regression model. The variance inflation factor (VIF) is calculated to estimate multicollinearity. From the evaluation it is found that the VIF is less than 10 which indicates there is no multi co-linearity in the observed data. Hence the model is nicely fitted for such data. The proposed research objective is to develop a statistical model which specifies the significance of diabetes mellitus in the risk factor analysis of NASH and CVD and we are trying to analyze the significance of the same in the coming days.

REFERENCES

1. Amiri, Nasrin et al.*Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis.* Gastroenterol Hepatol Bed Bench. Winter; 10(Suppl1): S1–S7,(2017)
2. Dai, Wenjie and the like. "Prevalence of Non-Alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus." Medicine (Baltimore). 96(39): e8179.
3. Dyson, J. K. et al. (2014). "Non-Alcoholic Fatty Liver Disease: A Practical. Approach to Treatment." *Frontline Gastroenterology* 2014;5:277–286
4. G., Targher *et al.* "Non-Alcoholic Fatty Liver Disease is Independently Associated with an Increased Incidence of Cardiovascular Events in Type 2 Diabetic Patients." *Diabetes Care* 2007;30:2119-21
5. H., Hagström et al. (2019). "Cardiovascular Risk Factors in Non-Alcoholic Fatty Liver Disease." *Liver Int*;39(1):197-204. doi: 10.1111/liv.13973.
6. Hazlehurst, Jonathan M. and the like (2016). "Non-Alcoholic Fatty Liver Disease and Diabetes." *Metabolism Clinical and Experimental*.65,1096-1108.
7. K. N., Bhatt et al. "Prevalence of Non-Alcoholic Fatty Liver Disease in Type 2 Diabetes Mellitus and its Relation with Insulin Resistance in South Gujarat Region." *J Mahatma Gandhi Inst Med Sci* 2017;22:8-11
8. M., Dharmalingam and Yamasandhi P. G. (2018). *Non-Alcoholic Fatty Liver Disease and Type 2 Diabetes Mellitus*. Indian J Endocr Metab ;22:421-8.
9. M., Prashanth et al. (2009). "Prevalence of Non-Alcoholic Fatty Liver Disease in Patients with Type 2 Diabetes Mellitus." *JAssociation of Physicians India*. 2009 Mar;57:205-10.
10. Mantovani, Alessandro, et al. (2018) "Non-Alcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-Analysis." *Diabetes Care*; 41(2): 372-382.

11. Patil, Rashmee and Gagan K. Sood (2017). "Non-Alcoholic Fatty Liver Disease and Cardiovascular Risk." *World J. Gastrointest Pathophysiol*. 2017 May 15; 8(2): 51–58.doi: 10.4291/wjgp.v8.i2.51. PMCID:PMC5437502
12. S. E., Mathews and the like (2018). Non-Alcoholic Steatohepatitis, Obesity, and Cardiac Dysfunction. 25(5):315-320. doi: 10.1097/MED.0000000000000432.
13. Tana, Claudio et al. (2019). "Cardiovascular Risk in Non-Alcoholic Fatty Liver Disease: Mechanisms and Therapeutic Implications." *Int. J. Environ. Res. Public Health* 2019, 16, 3104.
14. Targher, Giovanni et al. (2005). "Non-Alcoholic Fatty Liver Disease and Risk of Future Cardiovascular Events Among Type 2 Diabetic Patients." *Diabetes* 54:3541–3546, 2005
15. Wu, Shunquan and the like Fuquan Wu (2016). "Association of Non-Alcoholic Fatty Liver Disease with Major Adverse Cardiovascular Events: A Systematic Review and Meta-Analysis." *Scientific Reports*, Volume 6, Article Number: 33386.
16. Wong, Carrie R. and Joseph K. Lim(2018). "The Association between Non-Alcoholic Fatty Liver Disease and Cardiovascular Disease Outcomes."
17. Clin Liver Dis (Hoboken) v.12(2); PMC6385911. doi: 10.1002/cld.721 Wong, Carrie R. and Joseph K. Lim, (2018). "The Association between Non-A**l**coholic Fatty Liver Disease and Cardiovascular Disease Outcomes." *Clinical Liver Disease*, vol 12, No 2.