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ORIGINAL ARTICLE

ASSOCIATION OF NON-ALCOHOLIC FATTY LIVER DISEASE WITH GLYCEMIC CONTROL OF DIABETES IN NON- OBESE TYPE 2 DIABETIC PATIENTS

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Abstract:

Background: Non-alcoholic fatty liver disease (NAFLD) involves diffuse fat accumulation in hepatocyte and is frequently associated with metabolic conditions like obesity, Type 2 Diabetes Mellitus (T2DM), and hyperlipidemia. Despite its asymptomatic nature, NAFLD is commonly detected via ultrasonography, even in non-obese diabetic individuals. This study explores the relationship between NAFLD and diabetic glycemic control.

Objective: This research work assesses the association between NAFLD and glycemic control in non-obese Type 2 Diabetes Mellitus (T2DM) patients.

Material and Methods: A cross-sectional study was conducted on 100 diagnosed T2DM patients with BMI in range of 18.5±29.9 at DHQ TH DIK. The sample included 55 males and 45 females, with a mean age of 46.78 ± 8.39 years (range: 30–60 years). NAFLD was diagnosed via ultrasound, and glycemic control was evaluated using HbA1c, fasting blood sugar (FBS), and random blood sugar (RBS) levels.

Results: No significant association was found between NAFLD and HbA1c (p=0.826), FBS (p=0.778), or RBS (p=0.817), even without adjusting for confounders such as age, sex, BMI, medication, insulin use, and lipid levels.

Conclusion: NAFLD does not influence glycemic control in T2DM patients, as indicated by HbA1c, FBS, and RBS levels.

Keywords: Non-alcoholic fatty liver disease (NAFLD), Type 2 diabetes mellitus (T2DM), hyperglycemia, fasting blood sugar (FBS) levels, Random blood sugar (RBS) levels, Glycosylated Hemoglobin (HbA1c).

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Introduction:

Fatty liver or hepatic steatosis is featured by the existence of diffuse aggregation of fat in hepatocyte. People with fatty liver, who have not consumed alcohol in a significant amount in the past, are said to have Non-alcoholic fatty liver disease (NAFLD).[1] There are two mild forms of NAFLD, pure steatosis and non-alcoholic steatohepatitis (NASH), which may advance to more severe issues like cirrhosis and hepatocellular carcinoma. It has been studied that NAFLD has a robust relationship with obesity, T2DM or metabolic dysregulation.[2] Furthermore, hyperinsulinemia (because of peripheral insulin resistance), hypertension, and hypertriglyceridemia are metabolic syndrome indications which are all associated with its hepatic constituent.[3] Diabetic and obese people account for the higher prevalence of NAFLD.4 NAFLD is prevalent 10% among subjects with healthy (BMI) contrasted with 80% among obese, which shows its relation with BMI.[5] Fatty liver has an impact on the seriousness of hepatic insulin resistance in T2DM. [6] There is likewise a connection of hepatic insulin resistance with impaired fasting glucose levels (IFG).[7] A term "silent liver disease" is used for NAFLD because it is, for the most part, symptomless or diagnosed inadvertently by somewhat raised values of serum aminotransferase level or enlarged liver (hepatomegaly).[8] Histological, NAFLD is characterized by the presence of simple steatosis.[9] To confirm the

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diagnosis of NAFLD, liver biopsy, and histological assessment are done. In any case, a biopsy is usually avoided because the procedure isn't just intrusive and costly but may cause complications too. On the other hand, various non-invasive radiological imaging techniques like sonography, computed tomography (CT), or magnetic resonance imaging (MRI) are used to visualize the liver. The sensitivity and specificity of ultrasonography for the diagnosis of NAFLD is 80% and 99%,respectively, and it is generally utilized because it is inexpensive and readily available.[4,10] Moreover, it gives practically comparative outcomes as CT, MRI, or MRS, which are viewed as increasingly modern highest quality level imaging procedures.

NAFLD is highly prevailing in the developed world (around 30%); that's why it is gaining much consideration [1,11] and is on the head of the common hepatic disorders in the United States.[12] In Pakistan, hepatitis B and Cviruses[13] are the predominant causes of liver diseases. on-alcoholic fatty liver disease (NAFLD) is characterized by features such as increased hepatic echo texture, significant vascular blurring, and brightness observed on ultrasound. [14] While NAFLD has been extensively studied in Western countries, it remains largely asymptomatic and is rarely identified in Asian populations, with limited clinical data available on this condition. [15,16,17] Research, however, highlights a connection between NAFLD and the development of type 2 diabetes mellitus (T2DM) as well as obesity.[18] In this context, we investigated the relationship between NAFLD and glycemic control in non-obese patients with T2DM.

Material and Method:

This investigation was a cross-sectional observational type. The participants included were confirmed cases of T2DM, both males and females, with the age limit between 30-60 years and a BMI ranging from 18.5 to 29.9. The outpatient department of District Headquarter Hospital Dera Ismail Khan, Pakistan, was selected as the site for this study. The samples were taken during a half year's span; March 2016 to August 2016. The Institutional Review Committee gave approval for the protocol, and informed consent was taken from every participant before starting the study.

Study inclusion criteria:

The OPD visiting patients of both genders were involved in the study, who were known cases of T2DM without any history of co morbidity. The BMI range for the subjects was chosen between 18.5 and 29.9. The age limit was between 30-60 years.

Study exclusion criteria:

Patients with a history of alcohol utilization (daily alcohol utilization > 20g in females and > 30g in guys) as well as medications causing fatty liver were rejected. Besides, subjects who were anemic, pregnant, suffering from chronic hepatitis (HBsAg or Anti HCV positive) and kidneys, as well as heart disorders, were not selected in the investigation. Informed consent was obtained from all the members before consideration in the research. Patients with hepatitis B and C were rejected utilizing a rapid test kit comprising of a test cassette. BMI below 18.5 and more than equivalent to 30 were rejected.

Sample size:

G*Power 3.1.9 was used to determine the size of the sample with a power of 0.80 and an α value of 0.05 and utilizing the mean and standard deviation of HbA1c taken from published research work. The sample size was 100 known cases of T2DM of both genders as already done in a study by Ijaz et al.[19]

Personal data collection:

Before consideration in the study, all the subjects were asked to give informed consent. A comprehensive therapeutic history, which also included medications for diabetes, was taken from them. All subjects were assessed for the presence of hepatomegaly and anthropometric estimations, including height, weight, and BMI (weight in kg/m2)].

Blood Sampling:

Venous blood specimens were collected and processed quickly by centrifugation at 3000 rpm for 10 min. We analyzed the clear supernatant and afterward stored byfreezingat −20 °C until tested for triglycerides (TGs), cholesterol, and HDL. Cobas C501 was used for analysis. Blood samples were obtained in EDTA tube filled with anticoagulant, for the analysis of HbA1c and full blood count, by Cobas C501. Accu- Chek (Roche) glucometer was used to measure plasma fasting glucose (mg/dl) and 2 hours post-prandial glucose (after breakfast) levels.

Radiological assessment:

The hepatic fat constituent was assessed by ultrasound (Sono ACE R3 Samsung Medison). A transducer (2-5 MHz recurrence) with convex facet was used to evaluate the fat content of the liver. A method developed by Kumar et al. for the scoring of fatty liver was used for the grading of the fatty penetration and seriousness of liver pathology. Participants were asked to lie down in supine position during ultrasound evaluation, and estimations were recorded in the expiration phase. The view of fatty liver was bright with relatively more echogenicity when contrasted with the right kidney. Steatosis was graded as per the following. [20]

Mild steatosis (I): more echogenic liver, normal-looking diaphragm, and intrahepatic vessels; moderate steatosis (II): moderately increased echogenicity, mildly clouded representation of diaphragm and intrahepatic vessels;

Severe steatosis (III): Highly echogenic, much-obscured view of the diaphragm and intrahepatic vessels.

Table 1: Comparison of anthropometric and metabolic parameters between patients with and without NAFLD			
VARIABLES VARIABLES	**NAFLD**		**p**
	YES (n=58)	NO (n=42)	
Age	46.6 ± 8.2	47 ± 8.8	0.843
Weight (Kgs)	73.2 ± 10.7	65.3 ± 10.1	<0.001
BMI	26.7 ± 2.8	24.5 ± 3.4	0.001
CHOLESTROL	182.8 ± 33.3	181.5 ± 39	0.856
HDL	35.4 ± 9.8	37.8 ± 9.3	0.232
LDL	109.2 ± 24.8	108.5 ± 22.9	0.879
FBS	156.8 ± 46.2	159.6 ± 52.7	0.778
RBS	214.6 ± 70.6	218 ± 75.8	0.817
HbA1c	7.7 ± 1.3	7.7 ± 1.1	0.826
TGs †	162.52(145.38-181.68)	151.77(129.48-177.87)	0.466

Statistical analysis: Data was collected from patients using a patient information sheet and recorded in Microsoft Excel. The dataset was then cleaned to identify and address any missing values, abnormal entries, logical inconsistencies, or misplaced data. Discrepancies were cross-verified by consulting the original information sheets. Statistical analysis was conducted using SPSS version 22. To assess the normality of the data, Kolmogorov-Smirnov and Shapiro-Wilk tests were applied alongside histogram evaluations. As triglycerides were not normally distributed, they were log-transformed prior to analysis. Descriptive statistics, including percentages and mean ± SD, were used to summarize the data. An independent sample T-test was utilized to compare continuous variables such as age, weight, BMI, cholesterol, HDL, LDL, triglycerides, fasting blood sugar (FBS), random blood sugar (RBS), and HbA1c across groups categorized by fatty liver status. Univariate and multivariate regression analyses were performed to determine whether NAFLD was independently associated with blood glucose levels and HbA1c. A p-value of less than 0.05 was considered statistically significant.

Results:

In the current study, hundred (100) non-obese known cases of T2DM were included. Among these, males were 55, and females were 45 in number. Data of all the parameters were normally distributed except for AST, ALT, TGs, and urea, which were log-transformed for analysis. There was no statistical difference between NAFLD Yes/No groups for age, lipids, fasting, and post-prandial glucose levels and HbA1c (all p >0.05). However, NAFLD positive participants were heavier (Yes;73.2± 10.7kgvs. No; 65.3 ±10.1 kg, p= <0.001) and having higher BMI (Yes; 26.7 ± 2.8 vs. No; 24.5 ± 3.4, p= 0.001) (Table 1).

Values are mean ± SD. p for independent sample T-test comparison between presence and absence of NAFLD.

To check an independent relation of NAFLD with HbA1c, fasting, and random blood glucose levels, univariate and multiple regression analysis was done. There was no significant relation of NAFLD with HbA1c (Beta 0.022 and p=0.826) even without any adjustment (Table 2).

Table 2: "Impact of NAFLD on HbA1c Levels with Adjustment for Various Factors"			
Model Independent: NAFLD Dependent: HbA1c			
Total population (100)			
Adjustment factors	R2	Beta	P
-	.000	.022	0.826
Model 1+ Age	.017	.025	0.806
Model 2 + Sex	.017	.024	0.816
Model 3 + BMI	.017	.021	0.845
Model 4 + Metformin	.037	.016	0.885
Model 5+ Sulfonylurea	.037	.015	0.892
Model 6+ Insulin	.066	.036	0.744
Model 7+ FBS	.194	.047	0.644
Model 8+ RBS	.396	.029	0.742
Model 9+ LDL, HDL, Cholesterol, TG	.414	.026	0.771

After adjustment for confounders the relationship remained non-significant (R2= 0.414, p=0.771). Likewise, NAFLD was not related to fasting (Table 3)

Table 3: "Impact of NAFLD on Fasting Blood Sugar Levels with Adjustment for Various Factors"			
Model Independent: NAFLD Dependent: FBS			
Total population (100)			
Adjustment factors	R2	Beta	P
-	.001	-.029	0.778
Model 1+ Age	.021	-.031	0.755
Model 2 + Sex	.023	-.344	0.731
Model 3 + BMI	.028	-.008	0938
Model 4 + Metformin	.036	-.012	0913
Model 5+ Sulfonylurea	.040	-.022	0.839
Model 6+ Insulin	.045	-.032	0.774
Model 7+ RBS	.278	-.041	0.674
Model 8+ LDL, HDL, Cholesterol, TG	.523	-.014	0.862

And random glucose levels (Table 4) even without considering confounding variables.

Table 4: "Impact of NAFLD on Random Blood Sugar Levels with Adjustment for Various Factors"

Model Independent: NAFLD Dependent: RBS			
Total population (100)			
Adjustment factors	R2	Beta	P
-	.001	-.023	0.817
Model 1+ Age	.024	-.026	0.792
Model 2 + Sex	.027	-.31	0.758
Model 3 + BMI	.046	.018	0.869
Model 4 + Metformin	.081	.010	0.944
Model 5+ Sulfonylurea	.081	.008	0.941
Model 6+ Insulin	.088	.018	0.869
Model 7+ FBS	.310	.033	0.726
Model 8+ LDL, HDL, Cholesterol, TG	.424	.008	0.933

Discussion:

This study highlighted that, despite having a similar age range and mean, individuals with NAFLD were heavier and had a higher BMI, even though their BMI did not fall within the obese category (as obesity was excluded from the study criteria).

In this research, multiple regression analysis was performed to determine whether NAFLD was independently associated with HbA1c, FBS, and RBS. The findings showed no significant association between NAFLD and HbA1c (p=0.826) without any adjustments. Similarly, no link was observed between NAFLD and FBS or RBS, even without accounting for confounding factors.

In contrast, a study by Heidari et al. found a significant association between NAFLD (specifically Grades II and III) and HbA1c, FBS, BMI, triglycerides (TGs), LDL cholesterol, and the duration of diabetes.[21] The discrepancy in results may stem from differences in study populations. Heidari et al.'s research primarily included participants with Grade II or III NAFLD, whereas our study population had only 11 participants with Grade II NAFLD, with the majority being classified as Grade I.

In a prospective Australian cohort study conducted over 11 years (1994-95 to 2005), researchers examined the risk of developing diabetes in patients with NAFLD. The findings revealed that individuals diagnosed with NAFLD at the start of the study were three times more likely to develop diabetes compared to those without NAFLD.[22] similarly, a Korean study followed males with NAFLD for five years, demonstrating that NAFLD plays a predictive role in diabetes development. The severity of NAFLD, particularly moderate to severe cases, showed a strong association with Type 2 Diabetes Mellitus (T2DM).[23] Likewise, a 10-year observational study of middle-aged, healthy Japanese individuals of both sexes identified NAFLD as a significant predictor for diabetes development.[24]

Our study aimed to investigate whether NAFLD continues to have an impact after diabetes has already developed. To explore this, we analyzed diabetic individuals, focusing on diabetes-related parameters such as HbA1c, FBS, and RBS. We did not observe any independent association between NAFLD and these glycemic control parameters, suggesting that NAFLD does not influence blood glucose regulation after the onset of diabetes.

However, our study has certain limitations. While longitudinal studies are better suited to evaluate disease progression, ours was cross-sectional in nature. Additionally, although a biopsy and Histopathological examination are considered the gold standard for diagnosing NAFLD, we relied on ultrasound for its assessment. Most participants underwent an ultrasound for the first time after being diagnosed with diabetes and prior diagnostic records for NAFLD were unavailable.

Conclusion:

Our findings indicate that NAFLD does not influence diabetes control when assessed through HbA1c, FBS, and RBS levels, and therefore, it does not exacerbate T2DM. In summary, NAFLD appears to have no substantial impact following the onset of diabetes.

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