Cardiovascular Morbidity in Diabetic Non-Alcoholic Fatty Liver Disease (NAFLD) Using NAFLD Fibrosis Score as an Early Indicator

Erken Bir Gösterge Olarak Non-Alkolik Yağlı Karaciğer Hastalığı (NAYKH) Fibrozis Skoru Kullanılarak Diyabetik NAYKH'de Kardiyovasküler Morbidite

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Abstract

Objective: Rising prevalence of non-alcoholic fatty liver disease (NAFLD), its high incidence in diabetic patients, and global diabetes prevalence, underline the need to identify comorbidities in these patients impacting their quality of life and mortality. NAFLDis associated with increased risk, prevalence, and complications of cardiovascular diseases in diabetic and non-diabetics alike. The study aimed to establish a relationship between non-invasively assessed cardiovascular morbidity and NAFLD fibrosis score (NFS) in type 2 diabetes mellitus with NAFLD. **Material and Methods:** After ethical approval, the study was conducted (n=100) on patients <60 years of age, havingtype 2 diabetes mellitus, and no existing cardiovascular disease. All patients underwent anthropological and routine investigations, two-dimension (2D) echocardiography, and ultrasonographic confirmation of fatty liver disease. NAFLD was ascertained based on patient history and investigations. Findings of cardiovascular evaluation on 2D-echocardiography were assessed with reference to the NFS. **Results:** Median age of participants was 53.5 years. Body mass index (p<0.001), right carotid intima-media thickness (p=0.0124), and left ventricular dysfunction (p=0.0024) showed a significant association with NAFLD. The presence of both left ventricular diastolic dysfunction and significant variation of carotid intima-media thickness among mild, moderate, and severe NFS groups (p=0.0049) was observed. Patients with moderate-severe NFS had 6.38 times more risk of developing cardiovascular morbidities. **Conclusion:** In patients with type 2 diabetes and NAFLD, the NFS helps to identify those at high risk of cardiovascular disease, and patients needing further investigation. It provides clues on how non-invasive cardiovascular markers can be used in detecting cardiovascular morbidities.

Keywords: Cardiovascular diseases; carotid intima-media thickness; diabetes; non-alcoholic fatty liver disease; ventricular dysfunction

Özet

Amaç: Non-alkolik yağlı karaciğer hastalığının (NAYKH) artan prevalansı, diyabetik hastalardaki yüksek insidansı ve küresel diyabet prevalansı, bu hastalarda yaşam kalitelerini ve mortalitelerini etkileyen komorbiditelerin belirlenmesi ihtiyacının altını çizmektedir. NAYKH, hem diyabetiklerde hem de diyabetik olmayanlarda artan kardiyovasküler hastalık riski, prevalansı ve komplikasyonları ile ilişkilidir. Bu çalışmada, NAYKH olan Tip 2 diabetes mellitusta noninvaziv olarak değerlendirilen kardiyovasküler morbidite ile NAYKH fibrozis skoru (NFS) arasında bir ilişki kurmak amaçlanmıştır. **Gereç ve Yöntemler:** Çalışma, etik onay sonrası, Tip 2 diabetes mellitusu olan ve kardiyovasküler hastalığı olmayan 60 yaşın altındaki hastalar üzerinde gerçekleştirildi (n=100). Tüm hastalarda antropolojik ve rutin araştırmalar, iki boyutlu (2D) ekokardiyografi ve yağlı karaciğer hastalığının ultrasonografik doğrulaması yapıldı. NAYKH, hasta öyküsü ve araştırmalara göre belirlendi. 2D ekokardiyografide kardiyovasküler değerlendirme bulguları NFS referans alınarak değerlendirildi. **Bulgular:** Katılımcıların medyan yaşı 53,5 idi. Beden kitle indeksi (p<0,001), sağ karotis intima-media kalınlığı (p=0,0124) ve sol ventrikül disfonksiyonu (p=0,0024) NAYKH ile anlamlı bir ilişki gösterdi. Hafif, orta ve şiddetli NFS grupları arasında hem sol ventrikül diyastolik disfonksiyon hem de karotis intima-media kalınlığında anlamlı varyasyon gözlendi (p=0,0049). Orta-şiddetli NFS'li hastalarda kardiyovasküler morbidite geliştirme riski 6,38 kat daha fazlaydı. **Sonuç:** Tip 2 diyabetli ve NAYKH'li hastalarda NFS, yüksek kardiyovasküler hastalık riski taşıyan ve daha fazla araştırmaya ihtiyaç duyan hastaların belirlenmesine yardımcı olur. Non-invaziv kardiyovasküler belirteçlerin kardiyovasküler morbiditelerin saptanmasında nasıl kullanılabileceğine dair ipuçları sağlar.

Anahtar kelimeler: Kardiyovasküler hastalıklar; karotis intima-media kalınlığı; diyabet; non-alkolik yağlı karaciğer hastalığı; ventriküler disfonksiyon

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a broad term for liver diseases characterized by histological findings of 5% or greater macrovesicular steatosis of hepatocytes in individuals not consuming excessive alcohol (1). NAFLD can progress from a benign non-alcoholic fatty liver (NAFL) to a more severe form known as non-alcoholic steatohepatitis (NASH) associated with lobular inflammation and apoptosis. This further leads to fibrosis, cirrhosis, or even hepatic carcinoma in some cases (2). The prevalence of NAFLD is increasing in the world, including India. It affects around a quarter of the adult population, 60% of diabetic patients, and 90% of obese individuals (3). The current prevalence of NAFLD in the US and Asia isas high as 24.13% and 27.37%, respectively(4).In India, the prevalence of NAFLD is reported to be 9-32%(5). Individuals with type 2 diabetes mellitus (T2DM) have high incidences of NAFLD, and the current prevalence in the Indian population is 70%(6). The mortality rates in patients with T2DM due to cirrhosis have been reported to be significantly higher than the general population (7).

Evidently, NAFLD is associated with increased risk of cardiovascular diseases (CVD), atherosclerotic changes, and cardiac dysfunction such as left ventricular diastolic dysfunction (LVDD), especially in T2DM and obesity(4). Cardiovascular events in NAFLD are found to increase by 1.87-folds in existing T2DM.

Also, in patients with T2DM, NAFLD is associated with increased carotid wall thickening, early left ventricular diastolic dysfunction (LVDD), and reduced myocardial high-energy phosphate metabolism(8). NAFLD increases microvascular complications like chronic kidney disease in T2DM patients (9). The NAFLD fibrosis score (NFS) is a score based on age, blood sugar levels, body mass index (BMI), platelet count, albumin concentration, and levels of aspartate and alanine aminotransferases. It independently identifies NAFLD patients with and without advanced fibrosis at the time of diagnosis (10). Studies linking NAFLD and CVD underpin the need for exploring the relationship between cardiovascular (CV) dysfunction, NAFLD, and non-invasive markers. Non-invasive techniques like 2D echocardiography are optimal modalities to assess cardiovascular morbidity but are either costly or not available uniformly. We aimed to explore possible associations between NFS, and CV morbidity, by measuring carotid intima-media thickness (CIMT) and LVDD in the T2DM patients with NAFLD.

Material and Methods

This cross-sectional, descriptive study was undertaken at a tertiary care center in Maharashtra, India, after the approval of the Institutional Ethics Committee in accordance withthe principles of the Helsinki declaration. Simple consecutive sampling was used to investigate 154 patients of T2DM from whom written informed consent was obtained. Finally, a group of 100 patients was identified. Patients suffering from T2DM for more than five years, and <60 years of age were included in the study (11). Patients with a prior history of the cerebrovascular incident, myocardial infarction, ischemic heart disease,peripheral vascular disease, hepatic cirrhosis, pregnant women, smokers, patients with conditions causing atherosclerosis, patients on anticancer drugs, immunosuppressants, and steroids were excluded.

Routine clinical investigations (complete blood count, urea, creatinine, liver function tests) were performed. Participants were screened for fatty liver disease by ultrasonography, lipid profile (after 12-24 h of fasting), and viral markers HBsAg and anti-HCV-antibodies were detected on confirmation of fatty liver. NFS, a non-invasive scoring system, was used to estimate the amount of liver scarring. It is based on several laboratory tests. The formula for calculating NFS is $[-1.675+0.037\times$age (years) $+0.094\times$BMI $(kg/m^2)+1.13\times$IFG/diabetes (yes=1, no=0) $+0.99\times$AST/ALT ratio$-0.013\times$platelet $(\times10^9/L)$ -0.66 $\times$albumin (g/dL). This score is evaluated as <-1.455: a predictor of the absence of significant fibrosis (F0-F2 Fibrosis); ≤-1.455 to ≤0.675: intermediate score; >0.675: a predictor of the presence of significant fibrosis (F3-F4) (10,12).

LVDD was assessed by calculating the early (E) and late (A) diastolic filling velocities (E/A ratio) on M-Mode (values <1 and >2 considered abnormal). The normal deceler-

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ation time for E wave was taken in the range of 160-200 ms (values >200 and <160 considered abnormal). CIMT was determined by the carotid Doppler, and values ≥0.9 were considered abnormal.

Statistical analyses, i.e., simple and multiple linear regression, independent sample t-test, and chi-square test, were carried out for different variables to estimate the significant effects of these variables on NAFLD and R Studio version 1.2.5001, and significance (p-value) was set at <0.05.

Results

The male-female ratio of participants was 1.17 (n=100), with a median age of 53.5 years (Table 1). The majority of the participants were overweight or obese (median BMI=25.91). NAFLD fibrosis cut-off was categorized as mild, moderate, and severe, as described above. Average NFS for males and females were -0.4152±1.48 and -0.8004±1.49, respectively, with a mean significant difference (p=.043). However, no overall association between NFS and gender was observed (p>0.05).

According to 2D-ECHO, LVDD occurred in 44 patients, among whom mild, moderate, or severe NFS was detected in 10, 23, and 11 patients, respectively. In patients without LVDD, 21, 30, and 5 patients had mild, moderate, or severe NFS, respectively. No significant difference was observed in the distribution of NFS in the presence or absence of LVDD. However, a significant association was observed between the presence of LVDD and NFS (p=0.0022).

Mean CIMT showed a significantly increasing trend with respect to NFS categories (p=0.0025), and the highest mean CIMT was found in the moderate-severe fibrosis (F3-F4) category for the total population as well as for both genders (0.81, 0.84, and 0.93 in males and 0.81, 0.93 and 0.96 in females) for the mild, indeterminate and mod-

erate-severe groups, respectively. Multinomial logistic regression between CIMT and NFS (moderate and severe) with mild NFS as the reference category did not reveal any significant association between moderate NFS and CIMT (right and left). However, a significant association (p=0.0124) was observed between right CIMT and severe NFS, and no significant association was observed in left CIMT and severe NFS (Table 2).

When mild NFS and the absence of LVDD were considered as the reference category, no significant association between moderate NFS, CIMT (both right and left), and LVDD was observed. In contrast, a significant association was observed between severe NFS, right CIMT, and LVDD (p=0.0466), and no significant association was observed between severe NFS, left CIMT, and LVDD (Table 3).

Multinomial logistic regression of the presence of LVDD and NFS grades (mild fibrosis as the reference category) revealed significant association (p=0.0022), indicating that NAFLD related fibrosis is linked to the presence of LVDD.

The association between anthropometric parameters, biomarkers such as fasting blood sugar (FBS), postprandial blood sugar test (PPBS), hemoglobin A1c (HBA1c), and NFS indicated a significant association between BMI and NFS. However, no significant association was evident between other parameters (Table 4).

The correlation between the non-invasive cardiovascular markers and NFS calculated by Pearson's correlation revealed a significantly positive correlation between mild NFS and BMI, moderate NFS and left CIMT, and severe NFS and BMI. Although not significant, an interesting correlation pattern was noticed between mild, moderate, and severe NFS and right CIMT, FBS, PPBS, and HBA1c with varying strengths (Table 5).

Table 1. Demographic distribution of the study sample (n=100).				
Variable	**Mean ±SD**	**Minimum**	**Median**	**Maximum**
Age	52.81±4.96	42	53.5	60
Height	158.03±5.80	148	158	171
Weight	64.96±8.62	45	65	88
BMI	25.93±2.33	20.27	25.91	31.18

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Table 2. Association between NFS with CIMT-RT and CIMT-LT.

NAFLD-FS	Variable	Coefficients (P-value)
Moderate	Intercept	-0.04364 (0.8298)
	CIMT RT	2.6051 (0.2985)
	CIMT LT	-1.3826 (0.5676)
Severe	Intercept	-8.5608 (0.0038)
	CIMT RT	8.0468 (0.0124*)
	CIMT LT	1.0617 (0.7452)

CIMT RT: Carotid Intima Media Thickness Right; CIMT LT: Carotid Intima Media Thickness Left; *P significant at <0.05.

Table 3. Association between LVDD, CIMT (RT and LT), and NFS (moderate and severe).

NAFLD-FS	Variable	Coefficients (P-value)
Moderate	Intercept	0.734 (0.754)
	CIMT RT	1.6343 (0.541)
	CIMT LT	-2.0878 (0.408)
	Presence of LVDD	0.5843 (0.319)
Severe	Intercept	-7.1239 (0.030)
	CIMT RT	6.824 (0.046)*
	CIMT LT	0.1878 (0.956)
	Presence of LVDD	0.7609 (0.348)

CIMT RT: Carotid Intima-Media Thickness Right; CIMT LT: Carotid Intima-Media Thickness Left, LVDD: Left ventricular diastolic dysfunction; *P significant at <0.05.

The presence of both LVDD and CIMT varied significantly among mild, moderate, and severe NFS groups (p=0.0049). Additionally, the patients who had moderate-severe NFS had 6.38 times increased risk of developing CV morbidities as compared to the no-mild NFS group with as low as 0.53 as the risk for CV morbidities.

Discussion

The rising prevalence of NAFLD in India and around the globe and its high incidence in diabetic patients are public health challenges that need urgent attention. There is ever-mounting evidence that NAFLD is associated with increased risk, prevalence, and complications of CVD in diabetic and non-diabetics (4).

NAFLD is widely recognized as the hepatic component of metabolic syndrome, involving a plethora of metabolic abnormalities linked to visceral adiposity such as insulin resistance, hypertension, dyslipidemia, and hypertriglyceridemia (13). Both metabolic syndromeand NAFLD share common etiological factors such as sedentary lifestyle patterns, low-quality diet, and poor food choices (14). As many as 70-80%of T2DM patients have been shown to be afflicted with a condition in the NAFLD spectrum (4). The already increased CV risk in T2DM patients is further increased by the presence of NAFLD. Awareness and recognition of the quantum of risk of CVD before the onset of clinically apparent disease could aid inpro-

Table 4. Association between anthropometric parameters, biomarker (FBS, PPBS, HBA1c) and NAFLD-FS.

NFS	Variable	Coefficients
Moderate	Intercept	-4.7132 (0.0733)
	BMI	0.0997 (0.335)
	FBS	0.0039 (0.6266)
	PPBS	-0.0017 (0.7685)
	HBA1c	0.3801 (0.1040)
Severe	Intercept	-19.902 (0)
	BMI	0.4973 (p<0.001)
	FBS	-0.00895 (0.4429)
	PPBS	0.0139 (0.1296)
	HBA1c	0.6379 (0.0662)

*BMI: Body Mass Index; FBS: Fasting blood sugar; PPBS: Post Prandial Blood Sugar Test; HBA1c: Hemoglobin A1c; *P significant at <0.05.

Table 5. Correlation between the non-invasive cardiovascular markers and NAFLD-FS.

NFS	CIMT RT Pearson's Coefficient (P-value)	CIMT LT Pearson's Coefficient (P-value)	BMI Pearson's Coefficient (P-value)	FBS Pearson's Coefficient (P-value)	PPBS Pearson's Coefficient (P-value)	HBA1c Pearson's Coefficient (P-value)
Mild	0.2445 (0.1928)	0.1862 (0.3243)	0.3800 (0.0395)*	-0.787 (0.679)	0.0853 (0.6537)	0.067 (0.7223)
Moderate	0.2194 (0.1075)	0.3934 (0.0029)*	0.1635 (0.2329)	0.0832 (0.5498)	0.0612 (0.6567)	0.0487 (0.7236)
Severe	0.0696 (0.8052)	-0.4182 (0.1208)	0.5911 (0.0203)*	-0.2033 (0.4668)	-0.4721 (0.0756)	0.0977 (0.7288)

BMI: Body Mass Index; FBS: Fasting blood sugar; PPBS: Post Prandial Blood Sugar Test; HBA1c: Hemoglobin A1c; *P significant at <0.05; CIMT RT: Carotid Intima-Media Thickness Right; CIMT LT: Carotid Intima-Media Thickness Left.

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viding appropriate preventative treatment to the cohort at risk. The use of routine investigations as a surrogate guide for CV risk is a cost-effective strategy to recommend detailed investigations. This is especially important in countries like India, where healthcare is plagued by limited resources and predominant out-of-pocket health expenses. This study adds to the growing body of evidence available on NAFLD and morbidity due to CVD in T2DM.

Age is strongly correlated to NAFLD owing to mechanisms that increase hepatic fat accumulation, reflected in the mean age of 52.81 years of participants in this study and reported by Sivabal et al.(15). Age-related reduction in muscle mass and function coupled with deteriorating efficiency of the antioxidant system leads to an increase in oxidative stress, thereby promoting NAFLD (16).

The results of this study imply that NFS was not influenced by gender,although females had a significantly higher NFS score as compared to males. Conflicting trends are seen in other studies with respect to gender predilection. In studies by Kojima et al. and Suzuki et al., males were found to be more likely to develop NAFLD (17,18). However, in studies by Kalra et al. and Motamed et al., NAFLD was observed to be more prevalent in females than in males (19,20). In general, investigations of humans and animals have shown that the female sex is protected from NAFLD, owing to the positive effects of estrogen. Also, young females can partition fatty acids towardthe production of ketone bodies, rather than very-low-density lipoprotein (VLDL)-triacylglycerols, further bestowing protection against NAFLD (21).

BMI is also found to be closely linked with NAFLD, and a high median BMI of participants reflects this. The significant positive correlation of BMI with moderate and severe NFSis similar to the findings of Loomis et al. and Fan et al., who demonstrated BMI as a strong predictor of fatty liver disease (22,23). They emphasized the reduction of obesity for the prevention and management of NAFLD. In a meta-analysis comprising of 86 studies (8,515,431 patients, 22 countries), Younossi et al.showed 51% and 82% the prevalence of obesity in subjects with NAFLD and NASH, respectively (4). Particu-larly, age and BMI are components of the NFS, which probably explains the comparatively lower number of patients with mild fibrosis here.

CIMT and LVDD were used as non-invasive markers of CVD. CIMT reflects early atherosclerotic changes in the vascular system, while LVDD is a known marker of CV morbidities. There is a significant association between right CIMT and severe NFS, which indicates a strong link between NAFLD, NFS, and CV risk. The reason behind the difference between left CIMT and right CIMT is not clear but may be attributed to the difference in their anatomical origin, which in turn leads to a difference in flow intensities (24). No significant association between left CIMT and severe NFS can be justified to some extent. A study by Lankarani et al.observed that NAFLD patients have increased CIMT (25). Nahandi et al. reported a significant association between the presence of NAFLD and atherosclerosis, the combination also being a predictor of T2DM (26). Likewise, the presence of LVDD was also found to be significantly associated with NAFLD. Bonapace et al. deciphered that in patients with T2DM and NAFLD, early features of LVDD could be successfully detected by 2D-ECHO, similar to findings of this study (27).

In addition to the traditional CVD risk factors of age, BMI, and presence of T2DM, the presence of NAFLD in diabetic patients adds to the burden of risk. This study adds to the pool of knowledge by identifying the significantly increased CV risk in patients with moderate-severe NFS. Using the correlation between the NFS and measures of LVDD and CIMT, the role of NFS is postulated not merely to grade hepatic fibrosis but also to identify patients at increased CV risk.

Strengths and limitations

The cost-benefit ratio of advanced investigations is a matter of both ethical and financial concerns. The psychological stress of merely referring a patient for advanced investigations involvingradiological or cardiological assessments cannot be denied. Hence, it would be beneficial if investigations such as carotid doppler or 2D-ECHO are advised after preliminary screening. The

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NFS, platelet count, and liver function test (in addition to age, BMI, and diabetic status) offers a highly convenient method of screening asymptomatic patients of T2DM with NAFLD with no known CVD. In addition, assessing the correlation of insulin level with NFS and cardiac parameters would also be beneficial as an early indicator.

Conclusion

In T2DM patients with NAFLD, the NFS helps to identify those with CV morbidity, identifying patients who need further investigation. The highly significant correlation of cardiovascular risk, expressed as abnormal CIMT and/or LVDD, with moderate-severe NFS, offers NFS score as viable a screening tool for T2DM patients with NAFLD who are asymptomatic for CV disease. Further studies on similar lines, with larger sample size and varied age groups,are required to devise a precise model for predicting CV morbidity from NFS scores.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Priti Shahapure, Shimpa Sharma; Design: Priti Shahapure, Shimpa Sharma; Control/Supervision: Shimpa Sharma; Data Collection and/or Processing: Priti Shahapure; Analysis and/or Interpretation: Shimpa Sharma; Literature Review: Shimpa Sharma, Priti Shahapure; Writing the Article: Priti Shahapure, Shimpa Sharma; Critical Review: Shimpa Sharma; References and Fundings: Shimpa Sharma; Materials: Priti Shahapure.

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