Egyptian Journal of Medical Research

Print ISSN: 2682-4396 / Online ISSN: 2682-440X

Original article

Comparison between Non-alcoholic fatty liver disease Fibrosis Score in Diabetic and Non-diabetic Egyptian patients

Osama Mohamed Hammad[a], Alaa Farouk Haseeb[a], Manar Mahmoud Abdel Aziz[b], Michael Nady Naguib[a]

[a] *Endemic Medicine Department, Faculty of Medicine Beni-Suef University, Egypt*

[b] *Clinical and chemical Pathology Department, Faculty of Medicine Beni-Suef University, Egypt*

Article Info

Article history:

Received 17 February 2022

Accepted 2 March 2022

Corresponding Author:

Michael Nady Naguib

nadymichael64@gmail.com

Keywords

NAFLD

Type 2 Diabetes mellitus

NAFLD Fibrosis Score

Abstract

The aim of the present study was to compare NAFLD fibrosis score in diabetic and non-diabetic Egyptian patients to clarify the effect of diabetes on the development of fibrosis and NASH in NAFLD patients. This was a comparative anterospective observational study. 50 Egyptian patients with characteristic sonographic features and laboratory findings suggesting Non-alcoholic fatty liver disease were included. The patients were divided into two groups; Diabetic group and Non-diabetic group according to American diabetic association criteria 2015 comparing the NAFLD fibrosis score in both groups which uses six commonly measured parameters. Mean ±SD of NAFLD fibrosis score was -7.5± 0.97 in the non-diabetic group and 1.58± 1.9 in the diabetic group showing significant difference among the studied groups, as the lowest scores were in non-diabetic group, and the highest scores were in the diabetic group. This showing prevalence of advanced hepatic disease in Diabetic group more than non-diabetic group. The lower serum albumin and platelet count in combination with a higher AST to

ALT ratio seen with the DM patients reflect the higher prevalence of advanced fibrosis as they are recognized markers of hepatic synthetic function, portal hypertension and surrogates of advanced fibrosis respectively. We concluded that; more aggressive NAFLD as suggested by the higher NAFLD fibrosis score was seen in DM patients compared to non-DM patients

1. Introduction:

Hepatic steatosis is the first manifestation of a series of liver damage which may progress to steatohepatitis and finally, cirrhosis. It can exist as either a temporary or chronic state. Hepatic steatosis is characterized by a paucity of inflammation, cell death, or scarring and, importantly, is considered reversible. Estimates of the prevalence of hepatic steatosis are hard to make because it is typically asymptomatic, & a significant number of cases are undiagnosed. However, based on cross-sectional and autopsy studies, it is estimated to involve between 10 and 35 percent of population [1].

Once considered a benign condition, hepatic steatosis has acquired increased heed in recent years because of both of its association with obesity, diabetes and metabolic syndrome, as well as greater awareness of the potential to progress to steatohepatitis and cirrhosis, with an significant increase in the risk for hepatocellular carcinoma. In addition to these concerns, the importance of a significant proportion of fatty infiltration in liver transplant has fired interest in the non-invasive diagnosis and management of hepatic steatosis. However, the great majority of cases of NAFLD are linked with one or more elements of metabolic syndrome such as obesity and insulin resistance [2].

Hepatic steatosis is often first suspected when blood tests imply increased levels of liver transaminases. Indeed, NAFLD is the leading cause of abnormal liver enzymes in adults without an obvious cause of liver disease, and may in fact be the most prevalent overall cause of elevated liver enzymes in adult population. Enzyme values that may be elevated are usually restricted to alanine transaminase (ALT) and aspartate transaminase (AST). The decision to investigate hepatic steatosis must be made on the basis of a quantum of risk factors, involving elevated liver enzymes, if present, as well as obesity and other elements of metabolic syndrome [3].

Once suspected clinically, fatty infiltration of the liver should be established with imaging. Ultrasonography is boundlessly utilized as a first-line examination for hepatic steatosis

which supplies us with subjective evaluation of fatty penetration of the liver [4].

Although mostly not required for diagnosis, a liver biopsy is the crucial investigation for NAFLD and provides an estimation of hepatic steatosis, hepatocellular injury, inflammation and fibrosis [5].

The NAFLD fibrosis score is an accurate scoring system that includes six routinely measured parameters which are patient's age, BMI, impaired glucose intolerance, liver transaminases, platelet count and serum albumin. Advanced fibrosis can be reliably excluded (NPV 93%) using the low cut-off score (<−1.455) and diagnosed with high accuracy (PPV 90%) using the high cut-off score (>0.676). These results are validated in other studies [6].

Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) frequently coexist. The prevalence of NAFLD is estimated to be 59.67% in T2DM patients. This leads to unfavorable outcomes like higher rates of death due to cirrhosis. Cardiovascular events in NAFLD patients are increased by 1.87-fold in the presence of T2DM. NAFLD is connected with increased carotid intima-media thickness, increased coronary artery calcium score, early left ventricular diastolic dysfunction, decreased myocardial perfusion, and also decreased myocardial high-energy phosphate metabolism in patients with T2DM [7].

NAFLD is also known to increase microvascular complications of diabetes such as nephropathy and retinopathy. These pathological changes occur because of the release of pro-inflammatory, procoagulant, and pro-oxidant mediators, which had led to hepatic/systemic IR, atherogenic dyslipidemia, and the release of fetuin-A, fibroblast growthfactor-21, and retinol-binding protein-4 by liver. In the liver and skeletal muscle, fetuin-A binds and inhibits the insulin receptor tyrosine kinase, so inhibiting insulin signal transduction, leads to systemic and hepatic IR. Patients with diabetes or prediabetes had ongoing fibrosis when their serial biopsies were elaborated. It has been suggested that the progressive forms of NAFLD as NASH, advanced fibrosis, cirrhosis, and HCC happen mostly in this category [8].

The purpose of this study was to compare NAFLD fibrosis score in diabetic and non-diabetic Egyptian patients to illustrate the impact of diabetes on the occurrence of fibrosis and NASH in NAFLD patients.

2. Patients and Methods:

This was a comparative observational study was carried out on 50 Egyptian patients were collected from The Outpatient Clinic of Tropical Medicine Department, Beni-suef University Hospitals between June 2019 and December 2019.

2.1 The patients were divided into equal two groups: Diabetic group: 25 diabetic patients according to American diabetic association criteria 2015 with characteristic sonographic features and laboratory findings suggesting

NAFLD, and **Non-diabetic group:** 25 non-diabetic patients with characteristic sonographic features and laboratory findings suggesting NAFLD.

2.2 Laboratory findings suggesting NAFLD: Elevations in ALT and aspartate aminotransferase (AST) are typically mild when present and are usually not greater than three times the upper limit of normal. The ratio of AST/ALT is usually less than 1 in patients who have either no or minimal fibrosis, although this ratio may be greater than 1 with the development of cirrhosis.

2.3 Ethics:

This study was performed in compliance with the Helsinki Declaration after approval of the Research Ethical Committee of Beni-Suef University Hospitals and a written informed consent was obtained from all patients. Only patients fulfilling the inclusion criteria were included in the study.

2.4 Inclusion criteria:

1. Egyptian patients with characteristic sonographic features and laboratory findings suggesting NAFLD.
2. Age: older than 18 years.
3. Negative virology markers for HCV, HBV and acute HAV.
4. Considering Diabetic Patients: Type II diabetic patients diagnosed five to ten years prior to the study according to American diabetic association criteria 2015 as: Fasting plasma glucose (FPG) ≥126 mg/dl (7.0 mmol/L) Fasting is defined as no caloric intake for ≥ 8 hours. 2 Hours plasma glucose (2-hr PG) ≥200 mg/dl (11.1 mmol/L). Hemoglobin A1C ≥6.5% (48 mmol/l). Random plasma glucose (PG) ≥200 mg/dl (11.1 mmol/L) in individuals with symptoms of hyperglycemia.

2.5 Exclusion criteria:

1. Patients known to have liver cirrhosis.
2. Presence of other concomitant liver disease as: hemochromatosis, Wilson's disease, autoimmune hepatitis and primary biliary cirrhosis. These were excluded by specific laboratory tests.
3. Active alcohol intake (3 to 4 drinks every day).
4. Patients with positive markers for HCV, HBV and acute HAV.
5. Patients with T1DM.
6. Past history of malignancy.
7. Pregnancy and history of drug abuse.
8. Inability to provide written informed consent.

2.6 All patients were subjected to:

1) All patients were subjected to detailed history taking including age, sex, smoking status, body mass index (BMI), waist circumference and hip circumference, history of type 2 diabetes mellitus, type of anti-diabetic drug, alcohol intake, history of liver disease and viral hepatitis.

2) Clinical Examination including vital signs assessment, abdominal, chest and cardiac examination with special emphasis on

manifestations of LCF (jaundice, bleeding tendency, ascites and lower limb edema).

3) Laboratory investigations: serum samples were taken after overnight (12 hours) fasting in order to assess: Complete Blood Picture (CBC): Total leukocytic count, Hemoglobin, Hematocrit, platelet count. Liver function tests: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), serum albumin, bilirubin and INR. Fasting plasma glucose (FPG), random blood sugar, 2 hours post prandial blood sugar and HBA1C, and lipid profile.

4) Real Time Abdominal ultrasound with special emphasis on liver size, texture and hepatic veins. Presence of splenomegaly or calcular gall bladder.

2.7 Statistical Analysis:

SPSS version 19.0 for windows (SPSS Inc., Chicago, IL) was utilized for measurable investigation. All information were communicated as mean±SD or as number (rate) except if in any case showed, understudy's t-test will be utilized to think about mean and rate. One - way examination of change was utilized to think about quantitative boundaries, while Fischer's accurate test was utilized to analyze subjective boundaries. Factual importance was considered at $P<0.05$.

3. Results:

Table (1): The mean ± SD and range of the age and BMI of the studied groups.

Groups / Parameters	Diabetic group	Non-diabetic group	T- Test	P-value
Age (years) Mean± SD	46.8±14.7	53.9± 12.1	1.87	0.07
Range	28-81	22-84		
BMI Mean± SD	30.04±4.7	30.08± 3.7	0.03	0.97

Age in the diabetic group ranged from 28 years to 81 years with a mean± SD of 46.8±14.7 years while in the non-diabetic group was from 22 years to 84 years with a mean± SD of 53.9± 12.1 years. Mean ± SD and range of age among the studied groups showed no significant statistical difference. The Body Mass Index (BMI) (mean ± standard deviation) of diabetic group and non-diabetic group were 30.04±4.7 and 30.08± 3.7 Kg/m^2; respectively. Comparing mean values of the two groups revealed non-significant difference (P= 0.97) (Table 1).

Table (2): NAFLD Fibrosis Score in the studied patients.

Groups / NAFLD Fibrosis Score	Diabetic group	Non-diabetic group	T- Test	P-value
Mean± SD	1.58± 1.9	-7.5± 0.97	-5.48	**< 0.001**
95% CI	0.8 to 2.36	-1.16 to -0.36		
Range	-1.36 – 6.9	-2.86 - 0.67		
Median	1.92	0.51		

Calculation of NAFLD fibrosis score: −1.675 + 0.037 – age (years) + 0.094 – BMI (kg/m^2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet count (×10^9/l) – 0.66 × albumin (g/dl). Interpretation of NAFLD fibrosis score: In patients with an NAFLD fibrosis score above 0.676, the presence of advanced liver fibrosis can be diagnosed with high accuracy. In patients with an NAFLD fibrosis score below -1.455, advanced liver fibrosis can be excluded with high accuracy. Scores between -1.455 and 0.676 are considered "indeterminate." There was high statistically significant difference among the studied groups, as the lowest scores were in non-diabetic group, and the highest scores were in the diabetic group (Table 2).

NAFLD Severity Scale in the studied patients: Fibrosis Severity Scale: F0 = no fibrosis. F1 = mild fibrosis. F2 = moderate fibrosis. F3 = severe fibrosis. F4 = cirrhosis.

Table (3): NAFLD severity scale in the studied patients.

Groups / NAFLD Severity Scale		Diabetic group (n=25)	Non-diabetic group (n=25)	X^2	P-value
F0-F2	n (%)	1 (4%)	6 (24%)	24.8	**< 0.001**
Intermediate scale F2-F3	n (%)	6 (24%)	18 (72%)		
F3-F4	n (%)	18 (72%)	1 (4%)		

According to NAFLD severity scale, there was one (4 %) patient had F0-F2 stage of fibrosis in the diabetic group while there were 6 (24%) patients in the non-diabetic group. There were 6 (24%) patients in the diabetic group and 18 (72%) patients in the non-diabetic group that had intermediate scale (F2-F3). 18 (72%) patients in the diabetic group and only one (4%) patient in the non-diabetic group had F3-F4 stage of fibrosis. There was high statistically significant difference among the studied groups concerning NAFLD severity scale (Table 3).

Table (4): Pearson correlation coefficient between NAFLD fibrosis score and the age in the studied groups.

Variable	Age /years			
	Diabetic group (n=25)		Non-diabetic group (n=25)	
	Pearson correlation	P-value	Pearson correlation	P-value
NAFLD Fibrosis Score	0.63	**0.001**	0.21	0.31

There was significant proportional correlation between NAFLD Fibrosis Score and the age of diabetic group. The higher the age, the higher the NAFLD fibrosis score. While there is no significant correlation between NAFLD Fibrosis Score and the age of non-diabetic group (Table 4).

Table (5): Pearson correlation coefficient between NAFLD fibrosis score and the laboratory findings in the studied groups.

Parameter	NAFLD Fibrosis Score			
	Diabetic group (n=25)		Non-diabetic group (n=25)	
	Pearson correlation	P-value	Pearson correlation	P-value
AST (U/l)	0.08	0.13	0.25	0.91
ALT (U/l)	-0.31	0.13	-0.2	0.34
AST/ALT ratio	**0.72**	**< 0.001**	**0.42**	**.036**
Platelets ($x10^9$/L)	-0.78	**< 0.001**	-0.55	**0.004**
Albumin (gm/dl)	**-0.78**	**< 0.001**	-0.14	0.52

There was significant non-proportional correlation between NAFLD Fibrosis Score and the albumin level and platelets level in the diabetic group only. The higher the NAFLD fibrosis score, the lower the blood levels of albumin and platelets. Significant positive correlation between NAFLD Fibrosis Score and AST/ALT ratio in the diabetic group only. The higher the AST/ALT ratio, the higher the NAFLD fibrosis score. While there is no statistical significant correlation between NAFLD Fibrosis Score and the ALT and AST level in both groups (Table 5).

4. Discussion:

In the diabetic group, age of diabetic patient ranged from 28 years to 81 years with a mean± SD of 46.8±14.7 years, while in the non-diabetic group it ranged from 22 years to 84 years with a mean± SD of 53.9± 12.1 years with no significant statistical difference (P-value=0.07).

Regarding Body Mass Index (BMI) of diabetic group and non-diabetic group, were (30.04±4.7 and 30.08± 3.7 $Kg/m^{2)}$; respectively with no significant difference (P-value= 0.97).

Our results differed from Goh et al. [9] study who discussed the clinical characteristics of NAFLD patients with and without DM and accuracy of the NAFLD fibrosis score (NFS) in these two NAFLD groups. They found higher BMI in the diabetic group (37.16 ± 7.84) compared with the non-diabetic group (35.20 ± 8.84) with significant difference (P=0.03) between both groups. Simeone et al. [10] study showed that obesity (≥30 kg/m2) in the non-diabetic group was (63.6%) and (81.2%) for the diabetic group with significant difference (P=0.02).

Obesity was prevalent parameter in many studies which discussed the relation between NAFLD and diabetes as; in Singh et al. [11] study assessed the prevalence of NAFLD and advanced hepatic fibrosis in patients with T2DM using simple noninvasive scores; their NAFLD population accounting for 89% above normal weight limit, and Forlani et al. [12] who studied the prevalence of NAFLD and its clinical correlates in patients with type 2 diabetes mellitus T2DM and found that, their patients BMI were with mean ±SD of (30 ±6 Kg/m^2).

Nakahara et al. [13] study concluded that; there was association between obesity and fibrosis severity in NAFLD patients. As they compared the prevalence of obesity and the histological severity of NAFLD whereas the prevalence of obesity increased with the progression of fibrosis.

NAFLD fibrosis score:

Liver biopsy is the “gold standard” for NAFLD diagnosis; however, this is invasive and carries intrinsic morbidity risk. Ultrasonography is the recommended first-line imaging technique in clinical practice, although it is known to have limited sensitivity [11].

Recently, noninvasive scores have been developed to predict the presence of suspected NAFLD such as the hepatic steatosis index (HSI) [14].

Other scores were developed to predict advanced fibrosis such as the NAFLD fibrosis score (NFS), fibrosis-4 (FIB-4) index, aspartate aminotransferase (AST) to platelet ratio index (APRI) and AST/alanine aminotransferase (ALT) ratio [15, 16].

The NAFLD fibrosis score is a validated scoring system that comprises six routinely measured parameters which are patient's age, BMI, impaired fasting glucose, liver transaminases, platelet count and serum albumin [17].

The NFS was calculated according to the following formula-1.675+ [0.037×age (y)] + [0.094×BMI (kg/m2)] + (1.13 if diabetes) + (0.99×AST/ALT)—[0.013×platelet (109/L)]—[0.66×albumin (g/dL)]. A cutoff score 0.676 was used to diagnose advanced fibrosis [6].

Regarding NFS assessment in our study showed high statistically significant difference among the studied groups, as the lowest scores (-7.5± 0.97) were in non-diabetic group, and the highest scores (1.58± 1.9) were in the

diabetic group. This shows prevalence of advanced hepatic disease in diabetic group more than non-diabetic group (P-value< 0.001).

This agrees with many studies that used NFS showed advanced disease was more in diabetic patient as; Singh et al. [11] study with suspected NAFLD with determined scoring showed prevalence of advanced disease defined by NFS>0.676 was 35.4%, Forlani et al. [12] study which was 4.4%, and Lombardi et al. [18] study NFS was 22% of cases for diabetic patient.

In Goh et al. [9] study, it concluded that the NFS performed well in identifying patients with and without advanced fibrosis. However, subgroup analysis (diabetic and non-diabetic) suggested that the utility of the NFS had divergent clinical reliability for NAFLD patients with and without DM, particularly in excluding advanced fibrosis in patients without DM although this must be tampered in the context of a relatively lower prevalence of advanced fibrosis among the non-DM patients.

In general, patients with DM have higher risk of NAFLD, higher rates of NASH and advanced fibrosis relative to patients without DM [19].

In addition, DM is associated with accelerated progression of hepatic fibrosis, NAFLD patients with DM have twice the mortality risk compared to the general population with DM and no NAFLD [20].

Similarly, NAFLD patients with DM have three times the overall mortality risk and twenty-two times the liver related mortality risk compared to NAFLD patients without DM. In part, this mortality risk relationship is contributed by DM patients having a higher prevalence of NASH and advanced fibrosis [21].

Regarding Fibrosis Severity Scale, there was high statistically significant difference (P-value<0.001) among the studied groups concerning NAFLD severity scale, with higher severity scale in diabetic group (F3-F4).

These result in line with Goh et al. [9] study and Nakahara et al. [13] study who found that the prevalence of DM increased with progression of the fibrosis stage. Multivariate analysis identified DM as an independent risk factor for advanced fibrosis.

In vitro, high glucose and high insulin concentrations, which are often observed in patients with NAFLD, were shown to stimulate connective tissue growth factor expression, which is known as one of the important mechanisms involved in the progression of hepatic fibrosis [22].

Current study found a significant correlation between NAFLD Fibrosis Score and the albumin level and platelets level in diabetic patients only with a higher AST to ALT ratio of diabetic group.

Regarding AST to ALT ratio, there was high statistically significant difference (P-

value=0.042) among the studied groups concerning AST to ALT ratio, with higher ratio (1.78± 1.17) in diabetic group versus (1.23± 0.53) in the non-diabetic group.

The lower serum albumin (3.44±0.55 gm/dl) and platelet count (167.4±62.9 $x10^9$/L) in combination with a higher AST to ALT ratio seen with the DM patients reflect the higher prevalence of advanced fibrosis as they are recognized markers of hepatic synthetic function, portal hypertension and surrogates of advanced fibrosis respectively, in line with [15].

5. Conclusion:

The present study shows that more aggressive NAFLD as suggested by the higher NAFLD fibrosis score was seen in DM patients compared to non-DM patients.

Severe NAFLD in the DM patients was associated with obesity, older age, lower serum albumin and platelet count in combination with a higher AST to ALT ratio.

6. References:

1. Younossi ZM, Koenig AB, Abdelatif D, et al. (2016). Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology, 64(1):73–84.
2. Younossi Z, Anstee QM, Marietti M, et al. (2018). Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterology Hepatology, 15(1):11–20.
3. Xiao G, Zhu S, Xiao X, et al. (2017). Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. Hepatology, 66(5):1486–501.
4. Chalasani N, Younossi Z, Lavine JE, et al. (2012). The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology, 55:2005-2023.
5. Stinton LM, Loomba R. (2014). Recommendations for liver biopsy evaluation in non-alcoholic fatty liver disease. Minerva Gastroenterology Dietology, 60:5–13.
6. Angulo P, Hui JM, Marchesini G, et al. (2007). The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology, 45: 846-54.
7. EASL, Marchesini G, Day CP, et al. (2016). EASLEASD-EASO Clinical Practice Guidelines for the management of nonalcoholic fatty liver disease. J Hepatol., 64:1388–1402.
8. Bae JC, Rhee EJ, Lee WY, et al. (2011). Combined effect of nonalcoholic fatty liver

disease and impaired fasting glucose on the development of type 2 diabetes: A 4-year retrospective longitudinal study. Diabetes Care, 34(3):727–729.

9. Goh GB-B, Pagadala MR, Dasarathy J, et al. (2015). Clinical spectrum of non-alcoholic fatty liver disease in diabetic and non-diabetic patients. BBA Clinical, 2015(3): 141-5.
10. Simeone JC, Bae JP, Hoogwerf BJ, et al. (2017). Clinical course of nonalcoholic fatty liver disease: an assessment of severity, progression, and outcomes. Clin Epidemiol., 9: 679-88.
11. Singh A, Le P, Peerzada MM, et al. (2018). The utility of noninvasive scores in assessing the prevalence of nonalcoholic fatty liver disease and advanced fibrosis in type 2 diabetic patients. Journal of Clinical Gastroenterology, 52: 268-72.
12. Forlani G, Giorda C, Manti R, et al. (2016). The burden of NAFLD and its characteristics in a nationwide population with type 2 diabetes. Journal of Diabetes Research, 1: 1-6.
13. Nakahara T, Hyogo H, Yoneda M, et al. (2014). Type 2 diabetes mellitus is associated with the fibrosis severity in patients with nonalcoholic fatty liver disease in a large retrospective cohort of Japanese patients. Journal of Gastroenterology, 49: 1477-84.
14. Lee J-H, Kim D, Kim HJ, et al. (2010). Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Digestive and Liver Disease, 2010(42): 503-8.
15. McPherson S, Stewart SF, Henderson E, et al. (2010). Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut, 59: 1265-9.
16. Wai CT, Greenson JK, Fontana RJ, et al. (2003). A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology, 38: 518-26.
17. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. (2015). Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology, 149: 367-378.
18. Lombardi R, Airaghi L, Targher G, et al. (2020). NAFLD fibrosis score (NFS) can be used in outpatient services to identify chronic vascular complications besides advanced liver fibrosis in type 2 diabetes. Journal of Diabetes and its Complications, 34: 107-111.
19. Younossi ZM, Gramlich T, Matteoni CA, et al. (2004). Nonalcoholic fatty liver disease in patients with type 2 diabetes.

Clinical Gastroenterology and Hepatology, 2: 262-65.

20. Adams LA, Harmsen S, Sauver JLS, et al. (2010). Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: a community-based cohort study. The American Journal of Gastroenterology, 105: 1567-71.

21. Ekstedt M, Franzén LE, Mathiesen UL, et al. (2006). Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology, 44: 865-73.

22. Paradis V, Perlemuter G, Bonvoust F, et al. (2001). High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. Hepatology, 34: 738-44.