ORIGINAL ARTICLE
KLİNİK ARAŞTIRMA

Assessment of hepatosteatosis among diabetic and nondiabetic patients using biochemical parameters and noninvasive imaging techniques

Diyabetik ve nondiyabetik hepatosteatozlu hastalarda biyokimyasal parametreler ve noninvaziv görüntüleme verilerinin değerlendirilmesi

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SUMMARY

Aim: Nonalcoholic fatty liver disease (NAFLD) is considered the most common chronic liver disease in the general population. The higher mortality and morbidity among NAFLD patients and lack of symptoms makes early detection and management important. In our study, we aimed to evaluate the relationship between noninvasive imaging and biochemical markers in diabetic and nondiabetic patients diagnosed with NAFLD.

Material and Methods: The study was conducted from (September, 2017) to (December, 2017) on adults admitted to Internal Medicine and Gastroenterology outpatient clinics with hepatic steatosis reported on ultrasound or transient elastography within the last six months that exclude patients with other liver diseases or alcohol abuse. The data was collected and analyzed retrospectively. Number cruncher statistical system (NCSS) 2007 program was used for statistical analysis.

Results: 116 patients were included in this study. Diabetic patients compared to nondiabetics had significantly higher Controlled Attenuation Parameter (CAP), Liver Stiffness Measurement (LSM) and fibrosis values. Also, hypertension, hepatomegaly, high BMI, hypertriglyceridemia, hyperglycemia, high Hemoglobin A1c and hyperuricemia were found to be risk factors for NAFLD progression to fibrosis. Advanced fibrosis (F3, F4) was present in 18,6% of all our patients; 35,8% of diabetic and 5,7% of nondiabetic patients diagnosed with hepatic steatosis.

Conclusion: Transient elastography is now used in daily clinical practice as an accurate noninvasive tool during follow-up of patients with fatty liver. Early diagnosis of the stage of liver fibrosis improves monitoring and management of patients, especially in those with metabolic syndrome criteria.

Keywords: Diabetes, elastography, fatty liver, fibrosis, metabolic syndrome

ÖZET

Amaç: Nonalkolik yağlı karaciğer hastalığı (NAYKH) genel populasyonda en sık görülen kronik karaciğer hastalığıdır. Morbidite ve mortaliteyi artırması ve herhangi bir klinik semptom vermemesi, karaciğer yağlanmalarının erken tanı ve takibini önemli kılmaktadır. Çalışmamızda NAYKH tanısı almış olan diyabetik ve nondiyabetik hastalarımızın noninvaziv görüntüleme verileri ve biyokimyasal parametreleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Materyal ve Metodlar: Çalışmaya (Eylül, 2017 – Aralık, 2017) tarihlerinde İç Hastalıkları ve Gastroenteroloji polikliniklerine başvuran, son altı ay içinde ultrasonografi ve/veya transient elastografi ile hepatosteatoz tanısı almış olan erişkin yaş grubu hastalar dahil edilmiş; eşlik eden farklı bir karaciğer hastalığı olan ve alkol tüketmiş olan hastalar çalışmadan dışlanmıştır. Veriler retrospektif olarak değerlendirilmiştir. İstatistiksel veriler için NCSS 2007 programı kullanıldı.

Bulgular: Çalışmaya 116 hasta alındı. Diyabet tanısı olan hastaların CAP, LSM ve fibrozis değerleri, nondiyabetik gruptan anlamlı düzeyde yüksek bulundu. Yine hipertansiyon tanısı varlığı, hepatomegali olması, BMI, trigliserid düzeyi, kan Şekeri yüksekliği, Hemoglobin A1c ve ürik asit düzeylerinin de NAYKH ve fibrozis sürecini olumsuz yönde etkilediği görüldü.

Sonuç: Karaciğer yağlanmasının takibinde transient elastografi güvenilir sonuçlar veren noninvaziv bir teknik olarak günlük pratiğimize girmiştir. Özellikle metabolik sendrom kriterleri olan hastalarda fibrozis derecesinin erken dönemde belirlenmesi, takip ve tedaviye yön vermesi açısından önemlidir.

Anahtar kelimeler: Diyabet, elastografi, fibrozis, karaciğer yağlanması, metabolik sendrom

INTRODUCTION

Hepatosteatosis can be demonstrated radiologically and/or histologically. Nonalcoholic steatohepatitis (NASH) is the progressive form of disease, and can result with cirrhosis and hepatocellular carcinoma. Studies investigating the natural history of the disease have shown that 42% of patients had progression, 40% remained stable and 18% had regression (1). The most significant factor predicting progression to fibrosis is whether the patient is diabetic or not (2). A meta-analysis in 2017 concluded that mortality increases with increase in fibrosis stage (3). As the stage of liver fibrosis guides clinical management, its precise determination is crucial. Although liver biopsy is the gold standard for diagnosing liver fibrosis, it has its own limitations such as complications because of the invasiveness of the procedure, sampling errors and intraobserver variation in liver biopsy interpretations (4).

All these disadvantages ended up with the need for a reliable, repeatable and noninvasive methods for evaluating fibrosis. Nowadays, transient elastography is one of the techniques meeting these requirements. This technique provides calculating controlled attenuation parameter (CAP) and Liver Stiffness Measurement (LSM) values (5). The decrease in amplitude of ultrasound as it is propagated through the liver tissue can be estimated using the same radio-frequency data that are used for estimation of LSM using transient elastography and is called controlled attenuation parameter (CAP) (6). CAP provides an accurate and noninvasive estimation of liver steatosis (5). LSM is an accurate, noninvasive tool to estimate the degree of fibrosis in patients with NAFLD.

The aim of this study is to compare the sonographic hepatosteatosis grades with the CAP values and fibrosis stages measured by transient elastography, to investigate the relationship between these values and variables that can contribute to fibrosis progression and to explore the association between the results and some biochemical parameters and demographic features. Because detection and assessment of the extent of liver fibrosis will guide the follow-up and treatment; the use of new reliable, noninvasive modalities with no complications will improve preventing progression of the disease.

MATERIAL AND METHODS

The study was approved by the ethics committee of the Kartal Dr. Lütfi Kırdar Training and Research Hospital of the University of Health Sciences (No: 2017/514/118/11 & Date: 28.11.2017). The sample consisted of 116 adult patients who were diagnosed with hepatic steatosis through ultrasonography and/or transient elastography in the last six months and followed up in the internal medicine and gastroenterology outpatient clinics of the hospital between September 2017 and December 2017. The data were analyzed retrospectively.

Participants were asked to provide information about their age, gender, height, weight, body mass index, components of the metabolic syndrome, medications and comorbidities; ultrasound and transient elastography reports and some laboratory parameters (fasting blood glucose level, fasting insulin level, fasting connecting peptide (C-peptide) level, urea, creatinine, leukocyte count, neutrophil and lymphocyte counts, platelet count, mean corpuscular volume (MCV), hemoglobin, lipid panel, serological testing for hepatitis B, hepatitis C and HIV (human immunodeficiency virüs), INR, PT, serum iron, total iron binding capacity, ferritin, vitamin B12, folate, transaminases, GGT, ALP, TSH, free T4 (fT4), ceruloplasmin, anti nuclear antibody (ANA), anti mitochondrial antibody (AMA), anti smooth muscle antibody (ASMA), anti-liver-kidney microsomal (LKM) antibody, total protein, albumin, total and direct bilirubin, erythrocyte sedimentation rate, C-reactive protein (CRP), uric acid) were evaluated. These provided the estimation of extent of disease and exclusion of the diseases in differential diagnosis of NAFLD. These data also provided calculation of NAFLD fibrosis score and FIB-4 score. NAFLD fibrosis score is obtained using the formula: -1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m2) + 1.13 x Impaired Fasting Glucose/diabetes (yes = 1, no = 0) + 0.99 x AST/ALT ratio – 0.013 x platelet (x109/l) – 0.66 x albumin (g/dl) (7). FIB-4 score is calculated using the formula age (years)×AST (U/L)/[PLT(109/L)×ALT1/2 (U/L)] (8).

Besides, relationship between these data and CAP and LSM values measured by transient elastography could be assessed. At least 10 validated measurements by transient elastography and Interquartile Range (IQR) / median ratio of less than or equal to 30% were considered reliable (9). Cutoff values (kPA) for F0, F1, F2 and F3 fibrosis stages were <6, ≥ 6 kPa, F2 ≥ 8 kPa (10), respectively. Cutoff values for F3 were ≥ 9.6 kPa and ≥ 9.3 kPa and for F4 were ≥ 11.5 kPa and ≥ 11.0 kPa with M and XL probes, respectively (11). The CAP cutoff value for diagnosing hepatosteatosis was 222 dB/m (9). Because our aim was to study patients with NAFLD, patients with another accompanying liver diseases or patients consuming alcohol above a certain amount (20 g/day in women, 30 g/day in men) were excluded. Statistical Analyses were performed by using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, United states of America (USA) fprogram. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used for analysis. Student's t test was used for the pairwise comparison of normally distributed variables. The Mann Whitney U test was used for the pairwise comparison of nonnormally distributed variables. Oneway Analysis Of Variance (ANOVA) was used for the pairwise comparison of two or more normally distributed variables. The Kruskal Wallis

Test was used for the pairwise comparison of two or more nonnormally distributed variables. Pearson Correlation Analysis and Spearman's Correlation Analysis were used to determine the correlations between variables. Pearson Chi Square, Fisher-Freeman-Halton, and Fisher's Exact tests were used to compare qualitative data. All data were evaluated as significant if the p-value is less than 0.05.

RESULTS

The sample consisted of 116 patients with NAFLD (54 diabetic, 62 nondiabetic). The diabetic group consisted of patients with Hemoglobin A1c (HbA1c) levels of ≥ 6.5% and/or receiving treatment for diabetes mellitus (DM). The two groups were similar in terms of age and gender (Table 1).

Table 1: Distribution of demographic characteristics

Demographic Characteristics		
Age (year)	Min-Max (Median) Mean±SD	23-90 (53) 52.57±11.84
Gender; n (%)	Woman Man	82 (70.7) 34 (29.3)
Body Height (cm) (n=93)	Min-Max (Median) Mean±SD	142-182 (160) 161.31±9.55
Body Weight (kg) (n=93)	Min-Max (Median) Mean±SD	55.6-130.4 (87.1) 88.08±15.16
BMI (kg/m2) (n=93)	Min-Max (Median) Mean±SD	22-48.1 (33) 33.91±5.43
	Overweight Obese Severely obese Morbidly obese	22 (23.7) 38 (40.8) 20 (21.5) 13 (14.0)
DM n (%)	No Yes	62 (53.4) 54 (46.6)
DM Duration (year) (n=32)	Min-Max (Median) Mean±SD	1-29 (5) 9.28±8.43

Fibrosis, CAP and LSM values did not significantly differ by age and gender (p>0.05). The higher the BMI, the higher the fibrosis, CAP and LSM values (p<0.01). Participants with diabetes had significantly higher fibrosis, CAP, and LSM values than those without diabetes (p<0.01) (Table 2). Advanced stage fibrosis (F3, F4) was 18.6%, 35.8% and 5.7% prevalent in participants with hepatic steatosis, diabetes, and those without diabetes. The higher the HbA1c, the higher the fibrosis, LSM (p<0.01) and CAP (p<0.05) values. Moreover, the higher the preprandial blood glucose and insulin, the higher the fibrosis, CAP, and LSM values (p<0.01).

Table 2: Difference in Fibrosis, CAP and LSM Values between Diabetic and Nondiabetic Patients

		Total	DM		P
			DM (-) (n=62)	DM (+) (n=54)	
Fibrosis (n=91)	Min-Max (Median) Mean±SD	0-4 (1) 1.23±1.21	0-4 (1) 0.81±0.98	0-4 (1) 1.82±1.27	0.001
	F0 F1 F2 F3 F4	31 (34.0) 30 (33.0) 13 (14.3) 12 (13.2) 5 (5.5)	26 (49.1) 15 (28.3) 9 (17.0) 2 (3.8) 1 (1.8)	5 (13.2) 15 (39.5) 4 (10.5) 10 (26.3) 4 (10.5)	
CAP (n=91)	Min-Max (Median) Mean±SD	196-400 (308) 301.22±43.25	213-373 (283) 288.15±39.06	196-400 (328.5) 319.45±42.65	0.001
LSM (n=91)	Min-Max (Median) Mean±SD	2.1-75 (6.1) 8.39±9.31	2.1-17.3 (5.3) 5.90±2.62	3.7-75 (6.8) 11.86±13.42	0.001

There was no significant difference in the prevalence of USG steatosis and hepatomegaly between participants using oral antidiabetic (OAD) drugs and those using insulin (p>0.05). There was no significant difference in fibrosis values on transient elastography between the two groups (p>0.05). There was no significant difference in LSM values between the two groups (p>0.05), however, participants using insulin had higher LSM values than those using OAD drugs. Participants using OAD drugs, however, had significantly higher CAP values than those using insulin (p<0.05). In terms of the effect of hypertension, which is a component of metabolic syndrome, on NAFLD, participants with hypertension had higher fibrosis, CAP, and LSM values than those without hypertension (p<0.01). There were statistically significant differences between USG steatosis levels and fibrosis, CAP, and LSM values (p<0.01). Pairwise comparisons were performed to determine between which groups the difference existed. Diabetic patients had significantly higher fibrosis, CAP, and LSM values than the nondiabetic patients (p<0.01). There were no statistically significant differences between the other groups (p>0.05). In USG, patients with hepatomegaly had significantly higher fibrosis, CAP, and LSM values than those without hepatomegaly (p<0.01). AST, ALT, and GGT values were positively correlated with fibrosis and LSM values (p<0.01). Of seventeen participants with advanced fibrosis (F3, F4), sixteen had 1.5 to 3-fold elevations in transaminases. AST, ALT, and GGT values were not significantly correlated with CAP values (p>0.05). Uric acid levels were significantly correlated with fibrosis and CAP values (p<0.05), but not with LSM values (p>0.05). CAP was not significantly correlated with total cholesterol, LDL and HDL values (p>0.05) but was positively correlated with triglyceride levels (p<0.01). There was no correlation between fibrosis and LSM values (p>0.05) which were the other two parameters that we evaluated in lipid profile and transient elastography. NAFLD Fibrosis and FIB-4 scores were positively correlated with fibrosis, CAP and LSM values (p <0.01).

DISCUSSION

Obesity and diabetes are well-known risk factors for the development of NAFLD, which is the most common chronic liver disease in the general population (12,13). Diabetes is believed to be the most important predictor of progression to cirrhosis in the spectrum ranging from hepatic steatosis to steatohepatitis, fibrosis, cirrhosis, and primary liver cancer. Diabetes increases morbidity and mortality, and therefore, its diagnosis and treatment is of key importance. There is neither a disease-specific clinical finding nor a single diagnostic test, therefore, more than one noninvasive and invasive methods are used to diagnose NAFLD. Laboratory results may be normal in patients with NAFLD, however, there may also be a slight increase in AST, ALT, GGT, and ALP levels among some patients. In cirrhotic cases, laboratory variables including albumin, bilirubin,

and prothrombin time may deviate. USG steatosis, which is the most widely used noninvasive imaging method in the diagnosis of the disease, has three grades. However, it is questionable how clinically meaningful and how valuable that grading is in disease monitoring. It is of paramount significance to determine the stage of fibrosis in patients with fatty liver as well as in those with chronic liver diseases for follow up. Biopsy is the gold standard in the evaluation of fibrosis but it has limitations such as procedural complications, sample errors, and differences in interpretation. Besides, such factors as disease course and response to treatment may require rebiopsy. Transient elastography which has been used in recent years to measure hepatic steatosis and tissue elasticity satisfies that need. This study evaluated the demographic characteristics, and biochemistry and imaging findings of 116 patients (54 diabetic, 62 non-diabetic) admitted to Internal Medicine and Gastroenterology outpatient clinics with hepatic steatosis reported on ultrasound or transient elastography within the last six months. Eskandar Hajiani et al. used transient elastography to compare liver stiffness in diabetic and non-diabetic patients and reported that the former had significantly higher values than the latter (14). The results indicated that significant fibrosis was more prevalent in diabetic patients, and therefore, elastography was recommended for their follow-up. Sporea I et al. designed a study to compare sonographic hepatic steatosis grades and fibrosis stages by transient elastography in patients with and without diabetes and found that diabetic patients had significantly higher hepatic steatosis gradients and fibrosis stages than non-diabetics (15). In line with the literature, our participants with diabetes also had significantly higher fibrosis stages than those without diabetes (p=0.001). The higher the preprandial blood glucose and HbA1c, the higher the fibrosis stage. This points to the effect of diabetes on NAFLD and a more rapid progression in uncontrolled diabetes. There was, however, no difference between participants using OAD drugs and those using insulin. Transient elastography is a noninvasive imaging method. However, biochemical markers, such as NAFLD fibrosis and Fib 4 scores, can also be used to determine the stages of liver fibrosis. In this study, NAFLD fibrosis and Fib 4 scores were correlated with fibrosis stages measured by elastography. This can be a useful way to avoid unnecessary biopsies in patients with low scores. The results also show that we can use those scores in daily practice. Numerous studies have focused on this subject matter which will continue to be relevant as new imaging methods and serum markers are used more and more widely. Participants with diabetes had significantly higher CAP scores, which indicate hepatic steatosis, than those without diabetes (p=0.001). Participants with diabetes had significantly higher LSM scores than those without diabetes (p=0.001). In other words, the three parameters measured by transient elastography were higher in participants with diabetes than in those without diabetes. The higher the fibrosis stages, the higher the levels of AST, ALT, GGT, and uric acid. High transaminases and GGT were consistent with hepatic steatosis. High uric acid wasregarded as a bystander of metabolic syndrome. The positive correlation of high TG and uric acid with CAP values was also consistent with impaired metabolic state. Similar to our results, a strong correlation has been reported between CAP and LSM values and uric acid level (16). Participants with hypertension had significantly higher fibrosis, CAP, and LSM values than those without hypertension. This shows that other components of the metabolic syndrome also play an active role in the progression to fibrosis. There was a strong correlation between the BMI values and fibrosis, CAP and LSM values. Kwok et al. (14) found that obesity was the strongest predictive of steatosis and that it was consistent with increased CAP and fibrosis stages (17). Participants with grade 2 steatosis had higher CAP and LSM values as well as fibrosis stages than those with grade 1 steatosis. CAP and LSM values were positively correlated with BMI. This, however, does not mean that ultrasound can be used to determine fibrosis.

Participants using OAD drugs had significantly higher CAP values than those using insulin ($p<0.05$). However, this result does not give any information about the independent effects of OAD and insulin on CAP level because some participants received both treatments.

Participants with hepatomegaly on ultrasound had significantly higher fibrosis and CAP values than those without hepatomegaly on ultrasound ($p<0.01$), which can be accounted for entirely by hepatic steatosis because biochemical tests showed that participants did not have any other liver diseases.

In conclusion, hepatic steatosis is the most common chronic liver disease which can progress to cirrhosis. Diabetes is believed to be the most important risk factor for the development of hepatic steatosis. The most accurate method to evaluate liver damage in patient follow-up is liver biopsy, which, however, has been replaced in recent years by noninvasive and reliable methods due to the risk of complications. One of those methods is transient elastography. There is no specific tests that can be used to diagnose hepatic steatosis. It is generally detected incidentally by ultrasound report or transaminitis. Therefore, early diagnosis of fibrosis and identification of patients at risk for cirrhosis are of paramount importance for healthcare professionals to take precautions involving diet, exercise and drugs.

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REFERENCES

1. Mcpherson S, Henderson E, Hardy T, Burt A, Day C, Anstee QM, et al. Natural history of NAFLD: A study of 108 patients with paired liver biopsies. Gut. 2014;63:A1–A288.
2. Bertot LC, Adams LA. The natural course of non-alcoholic fatty liverdisease.Int J Mol Sci. 2016;17(5):774.
3. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and metaanalysis. Hepatology. 2017;65(5):1557-1565.
4. Pathik P, Ravindra S, Ajay C, Prasad B, Jatin P, Prabha S. Fibroscanversus simple noninvasive screening tools in predicting fibrosis in high-risk nonalcoholic fattyliver disease patients from Western India. Annals of Gastroenterology. 2015;28(2): 281–286.
5. Sasso M, Beaugrand M, de Ledinghen V, Douvin C, Marcellin P, Poupon R, et al. Controlled attenuation parameter (CAP): a novel VCTE™ guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. UltrasoundMed Biol. 2010;36:1825-1835.
6. Yoneda M, Yoneda M, Fujita K, et al. Transient elastography in patients with non-alcoholic fatty liver disease (NAFLD). Gut. 2007; 56: 1330–1331.
7. Angulo P, Hui J.M, Marchesini G, Bugianesi E, George J. The NAFLD fibrosis score: anoninvasive system that ıdentifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846-854.
8. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, et al. FIB-4: an inexpensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. Hepatology. 2007;46(1):32-36.
9. Boursier J, Zarski JP, de Ledinghen V, Rousselet MC, Sturm M, Lebail B, et al. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology. 2013; 57(3):1182-1191.
10. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, et al.Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuationParameter and liver stiffness measurements: a prospective cohort study. Gut. 2016;65(8):1359-1368.
11. Yılmaz Y, Ergelen R, Akın H, İmeryüz N. Noninvasive detection of hepaticsteatosis in patients without ultrasonographic evidence of fatty liver using the controlled attenuation parameter evaluated with transient elastography. European Journal of Gastroenterology and Hepatology. 2013; 25(11):1330-1334.
12. Setiawan VW, Stram DO, Porcel J, Lu SC, Le Marchand L, Noureddin M. Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: The multiethnic cohort. Hepatology. 2016;64(6):1969-1977.
13. Heidari Z, Gharebaghi A. Prevalence of non alcoholic fatty liverdisease and its association with diabetic nephropathy in patients with type 2 diabetes mellitus. J Clin Diagn Res. 2017;11(5):OC04–OC07.
14. Hajiani E, Alavinejad P, Hashemi SJ, Masjedizadeh AR, Shayesteh AA, Parishan F, et al. Comparison of the transient elastography (fibroscan) results among diabetic and non-diabetic patients with non-alcoholic fatty liver disease. Gastroenterol Hepatol. 2014;1(4):00021.
15. Sporea I, Mare R, Lupuşoru R, Sima A, Sirli R, Popescu A, et al. Liverstiffness evaluation by transient elastography in type 2 diabetes mellitus patients with ultrasound proven steatosis. J Gastrointestin Liver Dis. 2016;25(2):167-174.
16. Mikolasevic I, Milic S, Turk Wensveen T, Grgic I, Jakopcic I, Stimac D, et al. Nonalcoholic fatty liver disease – A multisystem disease?. World J Gastroenterol. 2016;22(43):9488–9505.
17. Kwok R, Choi KC, Wong GL, Zhang Y, Chan HL, Luk AO, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut. 2016;65(8):1359-68.