Feasibility of Fibroscan in Assessment of Hepatic Steatosis and Fibrosis in Obese Patients: Report From a General Internal Medicine Clinic

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ABSTRACT

Background: *In metabolic associated fatty liver disease (MAFLD) vibration controlled transient elastography (VCTE) by Fibroscan has emerged as a non-invasive diagnostic tool for the measurement of controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), which are surrogate markers for hepatic steatosis and fibrosis, respectively. However, obesity constitutes a limitation in terms of creating unreliable examinations due to increased skin to liver capsule distance. Here, we aimed to investigate the feasibility of VCTE in the evaluation of hepatic steatosis and fibrosis in obese individuals.*

Methods: *A total of 126 consecutive obese patients (body mass index ≥30 kg/m^2) without a known history of MAFLD enrolled in the study. We performed CAP and LSM measurements and calculated Fibrosis-4 Index for each patient and included data of those patients to the analysis, from whom valid measurements were able to be taken.*

Results: *Reliable VCTE measurements were able to be obtained in 122 patients (97%), from those in 34 patients with M and 88 patients in XL probe (median age: 50 [18-75], 45 males and 77 females). In 1 patient VCTE failed to take any measurements and in 3 the measurements were classified as unreliable. The mean CAP value was 323 ± 48 dB/m and the median LSM value 5.3 [1.8-34.3] kPa.*

Conclusion: *CAP and LSM assessments by Fibroscan are reliable diagnostic tools for the early diagnosis of hepatic steatosis and fibrosis in obese individuals.*

Keywords: *Obesity, fatty liver, fibrosis, metabolic syndrome*

INTRODUCTION

Vibration controlled transient elastography (VCTE) by Fibroscan has emerged for the assessment of hepatic fibrosis more than a decade ago[1] and since then widely used for estimation of hepatic fat quantity in addition to fibrosis in non-alcoholic fatty liver disease (NAFLD), recently renamed as metabolic associated fatty liver disease (MAFLD).[2] In this context, liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) obtained by VCTE are surrogate markers for hepatic fibrosis and steatosis, respectively.[3,4] Considering the significant impact of obesity in the progression of MAFLD in terms of the development of advanced fibrosis, a timely diagnosis and strict follow-up constitute a major clinical aspect in daily clinical settings.[5]

Albeit its excellent diagnostic accuracy, obesity constitutes a limitation in VCTE examinations due to the increased distance between liver capsule and skin, which created a necessity in the modification of the tool. For those individuals, an XL probe was developed which can reach deeper liver tissue and showed a significantly higher reliable measurement rate compared to the standard M probe for both LSM[6,7] and CAP examinations.[8,9] Despite this improvement in the diagnostic capability of the device, there is a lack of knowledge in the optimal cut-off of LSM and CAP, which can be applied to the general obese population, which may cause an under- or overestimation of the disease according to the chosen cut-off value.[10-16] Here, we aimed to investigate the feasibility of Fibroscan in obese patients and to define hepatic

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steatosis and fibrosis using the different LSM and CAP cut-offs recommended previously.

PATIENTS AND METHODS

Patients

A prospective study was conducted between July 2018 and July 2019 at the General Internal Medicine Clinics of Marmara University School of Medicine. We enrolled a total of 126 obese patients consecutively without a known history of hepatic steatosis, who were accepted to participate in the study. The clinical and laboratory parameters were recorded. The exclusion criteria were described in detail, previously.[15]

The MAFLD was defined as evidence of hepatic steatosis in addition to overweight or obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation parameters.[2] Obesity was classified according to the World Health Organization criteria and a body mass index (BMI) ≥ 30 kg/m^2, <35 kg/m^2 was classified as obesity class I, ≥35 kg/m^2, <40 kg/m^2 obesity class II, and ≥40 kg/m^2 obesity class III.[17] Bariatric surgery indication was defined as having class III obesity or class II obesity in addition to high-risk comorbid conditions, such as sleep apnea, diabetes mellitus, degenerative joint disease.[18] Metabolic syndrome was diagnosed following Adult Treatment Panel III criteria[19] and type 2 diabetes mellitus American Diabetes Association criteria.[20] According to the reference thresholds of our laboratory, the elevated aspartate transaminase (AST) and alanine transaminase (ALT) levels were defined as >37 U/L and >40 U/L, respectively.[21]

Vibration Controlled Transient Elastography

The VCTE examinations were performed with the FibroScan 502 Touch device (Echosens SA, Paris, France) by a single operator (YY) following a minimum of 3 h of fasting in accordance with the manufacturer's instructions.[10,22,23] The operator was blinded to the clinical and laboratory data. All the examinations were started with an M probe. Prompted by the automatic probe selection tool displayed in real-time, which is based on the skin to liver capsule distance influenced by personal weight, the probe was switched to XL. The reliability of the VCTE measurement was based on reaching at least 10 valid measurements and an interquartile-range-to-median ratio of ≤0.3. The examinations which failed to fulfill these criteria were accepted as unreliable.[24] For the definition of presence of hepatic steatosis CAP cut-offs of ≥214 dB/m,[14] ≥222 dB/m,[15] ≥238 dB/m,[10] ≥302 dB/m,[16] and ≥308 dB/m[12] were used, respectively. To identify advanced fibrosis, we used the LSM cut-offs of LSM ≥ 9.3 kPa,[15] ≥9.7 kPa,[14] ≥11 kPa,[25] and ≥12.5 kPa,[11] respectively and for significant fibrosis LSM ≥ 7.25 kPa,[11] LSM ≥ 7.6 kPa,[12] LSM ≥ 8.2 kPa,[16] and LSM ≥ 8.95 kPa,[25] respectively.

Calculation of Fibrosis-4 Index

For the calculation of Fibrosis-4 Index (FIB-4) we used the universally accepted formula: age (years) × AST (U/L)/platelets (10^9/L) × √ALT (U/L).[26]

Statistical Analysis

The normality of the continuous variables was examined by the Kolmogorov–Smirnov test. The normally distributed data were presented as mean ± standard deviation and non-normally distributed data as median [minimum-maximum]. The comparison of normally distributed data was analyzed with Student's *t*-test, whereas non-normally distributed data with Mann–Whitney *U* test. The categorical data were presented counts and percentages and compared with the chi-square test. Multivariable stepwise linear regression analyses were used for the analysis of independent predictors of hepatic steatosis and fibrosis defined by CAP and LSM, respectively. All data analyses were performed with the IBM SPSS version 24 for Windows (IBM Corp, Armonk, New York) and were reported with 95% CIs. A 2-tailed $P < .05$ was considered statistically significant.

RESULTS

Characteristics of the Study Population

The study population, which was included in the analysis, consisted of 25 patients (20.5%) classified as class I obese, 46 (37.7%) as class II obese, and 51 (41.8%) as class III obese ($n=122$). General characteristics of the study population were summarized in Table 1. Among them, 54 patients (44%) and 27 patients (22%) were candidates for bariatric surgery for being obesity class III, and being obesity class II in addition to having high-risk comorbidity, respectively.

Vibration Controlled Transient Elastography

A total of 126 patients underwent VCTE examinations and a total of 122 (97%) reliable measurements were able to be taken. From those, in 1 patient VCTE was failed to take any measurements. In 3 patients, the measurements were classified as unreliable following our criteria. One measurement failure and 2 unreliable measurements were observed among patients with obesity

Table 1. General Characteristics of the Study Population ($n=122$)

Characteristics	
Age, median [minimum-maximum], years	50 [18-75]
Gender, male/female, n (%)	45 (36.9)/77 (63.1)
BMI, median [minimum-maximum], kg/m^2	38.7 [30.8-61.4]
Obesity class 1/2/3, n (%)	25 (20.5)/46 (37.7)/51 (41.8)
Metabolic syndrome (yes/no), n (%)	79 (64.8)/42 (35.2)
Type 2 diabetes mellitus (yes/no), n (%)	53 (43.4)/69 (56.6)
Hypertension (yes/no), n (%)	45 (36.9)/77 (63.1)
Hyperlipidemia (yes/no), n (%)	29 (23.8)/93 (76.2)
Smoking (yes/no), n (%)	24 (19.7)/98 (80.3)
Waist circumference, mean ± SD, cm	117.2 ± 12.24
Hip circumference, median [minimum-maximum], cm	121 [103-154]
Albumin, median [minimum-maximum], mg/dL	4.4 [3.7-8.0]
AST, median [minimum-maximum], U/L	19 [11-87]
ALT, median [minimum-maximum], U/L	24 [10-174]
Elevated AST >37, n (%)	18 (14.8)
Elevated ALT >40, n (%)	29 (23.8)
GGT, median [minimum-maximum], U/L	27 [11-451]
Total cholesterol, median [minimum-maximum], mg/dL	198 [108-306]
Triglycerides, median [minimum-maximum], mg/dL	141 [59-1836]
HDL cholesterol, mean ± SD, mg/dL	47 ± 11
LDL cholesterol, mean ± SD, mg/dL	124 ± 33
Platelets, mean ± SD, × 10^3 per µL	265 ± 65
Hemoglobin, mean ± SD, mg/dL	13.7 ± 1.6
Glucose, median [minimum-maximum], mg/dL	102 [56-299]
HOMA-IR, median [minimum-maximum]	4.5 [0.6-86.0]
HemoglobinA1c, median [minimum-maximum], %	6 [4.4-13.3]

SD, standard deviation; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostatic model assessment for the insulin resistance.

class 3 (5.9%), which corresponds to a reliable measurement rate of 94.1%. The mean findings from the VCTE examinations are presented in Table 2. The prevalence of hepatic steatosis, significant fibrosis, and advanced fibrosis according to the different CAP and LSM cut-off values assessed by VCTE classified according to obesity classes were depicted in Figure 1 and Table 3, respectively.

Hepatic steatosis

In univariate analysis CAP value was significantly associated with body weight ($P < .001$), BMI ($P < .001$), waist circumference ($P < .001$), hip circumference ($P = .002$), waist/height ratio ($P = .001$), smoking ($P = .034$), hemoglobin ($P = .01$), AST ($P = .01$), ALT ($P = .039$), gamma-glutamyl transferase (GGT) ($P = .01$), glycated hemoglobin ($P = .031$), LSM ($P = .005$), and the probe type ($P > .001$). In the multivariate logistic regression analysis based on the cut-off value of CAP ≥302 dB/m, the BMI (OR = 1.182; CI = 1.079-1.296; $P < .001$) and the hemoglobin (OR = 1.739; 99% CI = 1.082-2.795; $P = .022$) were determined as independent predictors of hepatic steatosis defined by VCTE.

Hepatic Fibrosis

Conducting the univariate analysis, LSM value was significantly associated with the body weight (rho = 0.193; $P = .033$), BMI (rho = 0.278; $P = .002$), and the waist/height ratio (rho = 0.208; $P = .022$), AST ($P < .001$), elevated ALT ($P = .001$), GGT (rho = 0.276; $P = .003$), glycated

Table 2. Vibration Controlled Transient Elastography Measurements of the Population ($n=122$)

Characteristics	
Probe type (M/XL), n (%)	33 (28)/85 (72)
Number of valid measurements, median [minimum-maximum]	10 [10-16]
LSM, median [minimum-maximum], kPa	5.3 [1.8-34.3]
LSM IQR, median [minimum-maximum]	0.8 [0-6.7]
IQR/M, mean ± SD	14.5 ± 8.0
CAP, median [minimum-maximum], dB/m	323 ± 48

LSM, liver stiffness measurement; IQR, interquartile range; SD, standard deviation; CAP, controlled attenuation parameter.

hemoglobin (rho=0.251; $P=.006$), Homeostatic Model Assessment for Insulin Resistance (rho=0.399; $P<.001$), fasting blood glucose (rho=0.210; $P=.021$), and the CAP value (rho=0.429; $P<.001$). We found a significant negative correlation between LSM value and high-density lipoprotein (rho=−0.271; $P=.003$). In the multivariate logistic regression analysis based on the cut-off value of LSM ≥ 8.2, the BMI (OR=1.249; %95 CI=1.108-1.408; $P<0,001$) was determined as the only independent predictor of significant fibrosis defined by VCTE.

Stepwise Approach

The patients with evidence of hepatic steatosis according to different CAP cut-off values were classified as low, indeterminate, and high risk of advanced fibrosis according to FIB-4. In 1 patient FIB-4 was not able to be calculated due to lack of data. The results are summarized in Table 4. Among all the patients classified as low risk of advanced fibrosis according to different CAP cut-offs 7, 5, 3, and 3 patients had advanced fibrosis according to cut-offs of 9.3, 9.7, 11, and 12.5 kPa, respectively. The patients who were classified as the indeterminate risk for advanced fibrosis 2 patients had advanced fibrosis according to LSM cut-offs of 9.3, 9.7, and 11 kPa, and 1 patient according to 12.5 kPa. One patient with a high risk of advanced fibrosis was classified as advanced fibrosis according to all cut-off values for LSM.

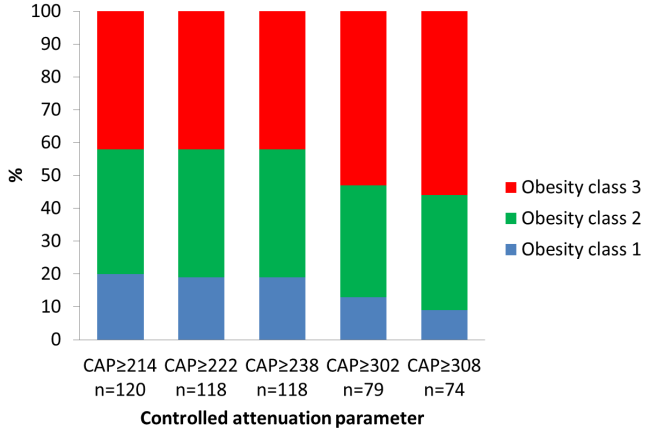

Figure 1. Prevalence of steatosis according to different CAP cut-offs assessed by VCTE. CAP, controlled attenuation parameter; VCTE, Vibration controlled transient elastography.

Table 3. Prevalence of Significant and Advanced Fibrosis According to Different LSM Cut-Offs Assessed by VTCE ($n=122$)

	Obesity class 1 ($N=25$), *N* (%)	Obesity class 2 ($N=46$), *N* (%)	Obesity class 3 ($N=51$), *N* (%)	Total ($N=122$), *N* (%)
LSM (kPa)				
Significant fibrosis F ≥ 2				
≥7.25	4 (16)	3 (6.5)	13 (25.5)	20 (16.4)
≥7.6	3 (12)	3 (6.5)	13 (25.5)	10 (8.2)
≥8.2	2 (8)	2 (4.3)	13 (25.5)	17 (13.9)
≥8.95	0 (0)	0 (0)	10 (19.6)	10 (8.2)
Advanced fibrosis F ≥ 3				
≥9.3	0 (0)	0 (0)	10 (19.6)	10 (8.2)
≥9.7	0 (0)	0 (0)	8 (15.7)	8 (6.6)
≥11	0 (0)	0 (0)	6 (11.8)	6 (4.9)
≥12.5	0 (0)	0 (0)	4 (7.8)	4 (3.3)

LSM, liver stiffness measurement; VCTE, vibration controlled transient elastography.

Table 4. Classification According to FIB-4 in Patients With Evidence of Hepatic Steatosis According to Different CAP Cut-Offs Assessed by VCTE

CAP (dB/m)	Low risk, *N* (%)	Indeterminate, *N* (%)	High risk, *N* (%)	*N* total
≥214	107 (89.9%)	11 (9.2%)	1 (0.8%)	119
≥222	105 (89.7%)	11 (9.4%)	1 (0.9%)	117
≥238	105 (89.7%)	11 (9.4%)	1 (0.9%)	117
≥302	70 (89.7%)	7 (9%)	1 (1.3%)	78
≥308	67 (91.8%)	5 (6.8%)	1 (1.4%)	73

FIB-4, fibrosis-4 index; CAP, controlled attenuation parameter; VCTE, vibration controlled transient elastography.

DISCUSSION

In this study, we found that CAP and LSM measurements by Fibroscan were able to assess hepatic steatosis and fibrosis among obese individuals with a relatively high reliable measurement rate of 97%. According to the different cut-off values reported previously, the prevalence of hepatic steatosis was 61-98%, significant fibrosis 8-16%, and advanced fibrosis 3-8%. In multivariate analysis hemoglobin and BMI were independent predictors of hepatic steatosis, whereas BMI remained the only independent predictor of significant fibrosis.

In the general population, the prevalence of MAFLD was reported as 13-31%.[27] On the other hand MAFLD shows a correlating trend with the increasing obesity severity. The prevalence of MAFLD reaches up to 65% in obesity class I-II and even 85% in class III obesity.[28] Moreover, obesity is associated with increased fibrosis stage and hepatocellular carcinoma.[29] Although the higher prevalence of MAFLD and a severer outcome of liver disease among obese individuals highlight a need to clearly define a screening strategy in obese individuals, there is no established strategy concerning that population. Here, we pointed out that issue.

In VCTE examinations, BMI was found as an independent predictor for measurement failure previously. This measurement failure corresponds to approximately 5-10% of the VCTE examinations in previous studies.[30,31] In our study, we showed a 3% of measurement failure which is possibly also significantly different than the previously reported values. We believe 1 of the possible reasons for this low rate of measurement failure is due to operator experience with a total of approximately 30 000 measurements, although we included a group of patients with a high obesity rate.

An XL probe has been emerged for reducing measurement failures in obese individuals and reaching higher reliable measurement rates.[7] It is well known, that weight loss is the only approved treatment of MAFLD, in terms of providing both remissions of steatosis and fibrosis.[32] Although liver biopsy is the reference standard in the assessment of liver disease, its use in clinical follow-up remains limited due to its invasive nature.[33] Therefore, the availability of an XL probe is of clinical importance in the accurate follow-up of obese individuals in treatment response.[34] In our study, we applied Fibroscan to obese patients with a 66% rate of indication for bariatric surgery and found adequate feasibility. In line with the previous studies, we also recommend the use of Fibroscan preoperative management of postoperative follow-up in those patients with an indication of bariatric surgery.[35,36] Although an XL probe enabled the applicability of Fibroscan in obese patients to some extent providing a greater distance of invasiveness >25 mm, there are still patients with a greater skin to liver capsule distance than 35 mm. To eliminate this, there is still an on-going trial for the enhancement of a probe with a better diagnostic performance in morbidly obese patients which corresponds to an XXL probe (ClinicalTrials.gov Identifier: NCT03872024).

The significant diagnostic accuracy and reproducibility of TE examinations make it an excellent diagnostic tool for the use of clinical settings. However, Fibroscan is not widely available and is not appropriate for the primary care settings, which makes first-line triaging crucial.[37,38] Therefore, previously a stepwise approach was recommended. Accordingly after the first-line stratification with FIB-4, in patients with indeterminate risk of advanced fibrosis further evaluation with TE was indicated.[25,39] Following the recommended approach, we were also able to avoid liver biopsy in more than 90% of the patients. Moreover, following that approach, we were able to diagnose 3 patients with advanced fibrosis after eliminating those patients with low risk of advanced fibrosis. In line with the previous data, we believe a liver biopsy would diagnose more patients with advanced fibrosis than those patients with an indeterminate or high risk of advanced fibrosis.[25]

Our results should be viewed in light of several limitations and strengths. Our study includes a lack of simultaneous liver biopsy, which was not performed due to ethical reasons. The sample size was also limited for an accurate evaluation. We also did not include a homogenous control group for obese individuals. Moreover, we invited 201 patients to the study. However, 75 patients refused to participate in our study, which may affect our results. Our limitations notwithstanding, the strength of this study lies in the fact that the examinations performed in an experience single-center with a total of more than 15 000 measurements by a single operator, who was blinded to the clinical history and laboratory examinations of the patients, and with a single device the FibroScan®502 Touch with regular machine inspections and validation.

In conclusion, CAP and LSM by Fibroscan are reliable and non-invasive diagnostic tools in the assessment of hepatic steatosis and fibrosis in obese individuals. For the

assessment of MAFLD in obese individuals, we highly recommend Fibroscan examination.

Ethics Committee Approval: This study was conducted in adherence to the Declaration of Helsinki and approved by our locak ethics committee with the following protocol number: 09.2017.223.

Informed Consent: Written informed consent was obtained from all the patients for the procedure.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.A., Y.Y.; Design - Y.Y.; Supervision - Y.Y., Resource - Y.Y.; Materials - A.A., E.K., Y.Y., Data Collection and/or Processing - A.A., E.K.; Analysis and/or Interpretation - A.A., E.K., Y.Y.; Literature Search - A.A., E.K., Y.Y.; Writing - A.A., E.K., Y.Y.; Critical Reviews - Y.Y.

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