JGH Open An open access journal of gastroenterology and hepatology Open Access

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12579

ORIGINAL ARTICLE

# Fibroscan® probe selection for lean adults

Vanessa Stadlbauer,* Iohanes Negrean,* Andreas Posch,* Andrea Streit,* Nicole Feldbacher,*,† Rudolf E Stauber* and Angela Horvath*,†

*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz and †Area 3 Cardiometabolic Health, Center for Biomarker Research in Medicine (CBmed), Graz, Austria

**Key words**
agreement, bias, examination, liver stiffness, meal, preparation, steatosis, thoracic circumference, transient elastography.

Accepted for publication 18 May 2021.

**Correspondence**
Vanessa Stadlbauer, Division of Gastroenterology und Hepatology, Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria.
Email: vanessa.stadlbauer@medunigraz.at

Vanessa Stadlbauer and Iohanes Negrean contributed equally to this study.

**Declaration of Conflict of interest**: The authors declare that they have no conflict of interest.

**Author contribution**: Vanessa Stadlbauer: Conceptualization, methodology, formal analysis, writing—original draft preparation, visualization. Iohanes Negrean: Investigation, data curation. Andreas Posch: Investigation, data curation. Andrea Streit: Investigation, data curation. Nicole Feldbacher: Investigation, data curation, project administration. Rudolf E. Stauber: Supervision, resources, writing—review and editing. Angela Horvath: Formal analysis, visualization, writing—review and editing.

## Abstract

**Background and Aim:** Fibroscan® is used to assess fibrosis and steatosis of the liver noninvasively. The company suggests to use the S+-probe in people <18 years with a thoracic circumference (TC) between 45 and 75 cm and the M+-probe in children with a TC >75 cm and adults with a skin–liver capsule distance <2.5 cm. For lean adults with a TC ≤75 cm, no comparative studies have been performed. Furthermore, it is unclear whether lean adults need to be fasted before assessment.
**Methods:** We compared liver stiffness (LS) using Fibroscan® S+- and M+-probes and controlled attenuation parameter (CAP; only available for M+-probe) in healthy volunteers with a TC ≤75 cm compared with those with a TC >75 cm in fasting state and after intake of a standardized light meal (300 kcal).
**Results:** We examined 50 volunteers (26 female, 24 ± 3 years). Twenty-two participants were in the TC ≤75 cm group and 28 in TC >75 cm group. LS values with the S+-probe were 15% higher than with the M+-probe in both groups (median difference 0.6 kPa, $P < 0.001$). Both probes showed good agreement with minimal bias (Spearman correlation $r = 0.754$, $P < 0.001$; Interclass Correlation Coefficient 0.843, $P < 0.001$; Bland–Altman bias 0.6 ± 0.9 kPa, linear regression $r^2 = 0.557$, $P < 0.001$). Intake of a light meal had no relevant influence on LS (S+- and M+-probes) or CAP measurements (M+-probe) in both groups.
**Conclusion:** Lean adults with a TC below 75 cm can be assessed with either the S+-probe or the M+-probe and may take a light meal before assessment.

## Introduction

Liver fibrosis and steatosis are important hallmarks of liver disease, and their assessment is an important diagnostic tool in hepatology. Currently, the gold standard is liver biopsy, an invasive and cost-intensive method that carries a certain risk of complications and may be inaccurate due to sampling error. Noninvasive, more cost-effective alternatives have been developed and validated in the past years, one of which is transient elastography, most commonly assessed using the Fibroscan device (Fibroscan, Echosens, France).[1–3] Fibroscan therefore has been integrated into clinical practice as a risk-free diagnostic tool for liver fibrosis and steatosis. With this device, it is possible to evaluate liver stiffness (LS) and controlled attenuation parameter (CAP) as a surrogate for steatosis.[4,5] The probes used for these measurements come in different sizes and are optimized for different body morphologies. In the user manual, the manufacturer provides an algorithm for the selection of the appropriate probe. This algorithm suggests to use the S+-probe in children with a thoracic circumference (TC) up to 75 cm, and the M+-probe in children with a TC above 75 cm and in nonobese adults with a skin–liver capsule distance of <2.5 cm. While in children TC is important to decide on the probe to be used, information on the influence of TC in nonobese adults is lacking. Adults with a skin–liver capsule distance of <2.5 cm may have a TC above or below 75 cm. For lean adults with a TC under 75 cm, it has not been studied yet, whether the S+-probe could or should be used. For patients with eating disorders or metabolic diseases and

women in general, who are more likely to have a TC under 75 cm, it is of importance to know the use of either probe would be possible or would introduce bias that needs to be accounted for. Comparative studies with M+- and XL-probes in adults showed that the XL-probe produces 20% lower LS measurements compared with the M+-probe.[6] M+- and S+-probes were so far only compared in a small group of children, showing that the S+-probe produced 10% higher results.[7] No comparison between the S+- and the M+- probes in adults has been published to date.

Incidentally, patients with eating disorders or metabolic diseases might also be challenged by the current recommendation to perform the assessment in a fasted state. Studies with the M+-probe indicated—although not uniformly—that food intake increases LS measurements in patients with chronic liver diseases with and without fibrosis and in healthy children. The increase in LS was attributed to postprandial hyperemia, but did not show a clear correlation with the ingested amount of calories.[7–13] Comparable studies in adults are lacking for the S+-probe to the best of our knowledge, although the information would be highly relevant, not only for vulnerable patient groups but also for the optimization of the hospitals' planning and logistics because examinations can then be scheduled at any time during the day.

The aim of the present study was therefore to close this knowledge gap and find a rationale for the most appropriate probe to use for lean adults with a TC below 75 cm. Furthermore, we aimed to assess the impact of a standardized light meal on LS and CAP measurements in healthy adults.

## Methods

***Participant selection.*** Healthy volunteers were recruited between June and October 2019 to participate in this study. Volunteers were included when they were at least 18 years old and gave written informed consent. Volunteers with history of acute or chronic liver disease and a skin–liver capsule distance above 2.5 cm were excluded. The study was approved by the institutional review board (31–245 ex 18/19) and registered at clinicaltrials.gov (NCT03947359) before inclusion of the first participant. The study was conducted according to the principles of the Declaration of Helsinki.

***Assessment of LS and CAP.*** LS and CAP were assessed with a Fibroscan 502 touch (Echosens, France) using the S+- and M+-probes according to the manufacturer's recommendations. Assessments were done after at least 6 h of fasting as well as 30, 60, and 120 min after the intake of 200 mL of Fresubin Energy (300 kcal, Fresenius Kabi, Germany) simulating a light breakfast. For the examination, the participants were lying on the back with the right arm above the head and measurements were performed on the right lobe of the liver in intercostal position. Both probes produce a vibration consisting of a sinusoid period with a center frequency of 50 Hz. Technical differences between the probes are listed in Table 1.

**Table 1** Technical differences between the S+- and the M+-probe

| | S+-probe | M+-probe |
|---|---|---|
| Central US frequency | 5 MHz | 3.5 MHz |
| External diameter of the tip | 5 mm | 7 mm |
| Peak-to peak amplitude | 1 mm | 2 mm |
| Measurement depth | 20–55 mm | 25–65 mm |

The median of at least 10 valid measurements and the measurements of variance were recorded. For LS, the interquartile range (IQR) as percentage of the median (IQR/median%) was used as measurement of variance, and the results were considered valid if IQR/median% was below 30%. For the M+-probe, LS below 6.0 kPa is considered normal.[14] For the S+ probe in adults, no normal range is defined. In a study of 270 children, the upper limit of normal (mean plus two standard deviations) was 6.5 kPa.[7] For CAP, the IQR was used as measurement of variance (IQR[CAP]) and a CAP below 275 dB/m was considered normal.[15] TC and body mass index (BMI) were recorded. Patients were stratified according to their TC into TC ≤75 cm and TC >75 cm.

***Statistical analysis.*** Data were analyzed using SPSS V26 (IBM, Armonk, NY, USA). Data are shown as median and 95% confidence interval (CI). When comparing two groups, Chi-square test, Mann–Whitney *U* test, or Wilcoxon test were used as appropriate and when comparing more than two groups Friedmann test with Bonferroni corrected post hoc analysis was applied. Comparison of measurements obtained with the two probes was performed with Bland–Altman test, Spearman correlation, interclass correlation coefficient, and linear regression. $P < 0.05$ was considered statistically significant.

## Results

***Subject characteristics.*** Fifty volunteers (26 female, 24 ± 3 years) were included, and two were excluded due to incidental finding of elevated liver function tests. TC measurements ranged from 58 to 99 cm. Twenty-two had a TC below 75 cm (TC ≤75 cm), and 28 had a TC above 75 cm (TC >75 cm). The TC ≤75 cm participants were mainly female ($n = 19$, $P < 0.001$) with lower BMI compared with the TC >75 cm group ($P < 0.001$).

***Comparison of LS and CAP in fasted state using S+-probe and M+ probe in healthy adults with TC ≤75 cm and TC >75 cm.*** LS measurements obtained with the S+-probe in fasted state were 15% higher than measurements obtained with the M+-probe from the same individual, with a median difference of 0.6 (IQR 1.4) kPa ($P < 0.001$). In the TC ≤75 cm group, the variance between measurements was comparable for both probes; however, in the TC >75 cm group, the measurements obtained with the S+-probe showed a higher variance than measurements obtained with the recommended M+-probe ($P = 0.002$). The agreement between measurements obtained with the different probes was good for the whole cohort (Spearman correlation $r = 0.754$, $P < 0.001$; Interclass Correlation Coefficient 0.843, $P < 0.001$; Bland–Altman bias 0.6 ± 0.9 kPa, linear regression $r^2 = 0.557$, $P < 0.001$). Similar agreement was found when the TC ≤75 cm and TC >75 cm groups were analyzed separately (data not shown).

LS was significantly lower in the TC ≤75 cm group compared with the TC >75 cm group measured with both the S+-and the M+-probes ($P = 0.041$ and $P = 0.028$, respectively).

Variance was comparable between the TC ≤75 cm and TC >75 cm groups for both probes. CAP and IQR(CAP) obtained by the M+ probe did not differ between the TC ≤75 cm group and the TC >75 cm group; this feature is not available for the S+-probe (Table 2).

***Influence of a light meal on LS and CAP measurements using S+-probe and M+ probe in healthy adults with TC ≤75 cm and TC >75 cm.*** Ingestion of a standardized light meal did not influence LS measurements in TC ≤75 cm participants obtained with either the S+- or the M+-probe. Same is true for measurements obtained with the M+-probe from TC >75 cm participants. When assessing LS in TC >75 cm participants using the S+-probe, a slight but significant drop of LS 60 min after the light meal compared with the previous time-point (30 min) could be observed; however, there was no significant change of LS relative to the fasted state (Fig. 1a,b). Measurements of variance did not differ over time in both groups. CAP decreased significantly 120 min after the meal compared with baseline in the TC ≤75 cm group but was unchanged by the meal in the TC >75 cm group. IQR(CAP) did not differ over time in both groups. (Fig. 1c).

**Table 2** Proband characteristics and LS and CAP measurements in participants with TC ≤75 cm and TC >75 cm

| | TC ≤75 ($n = 22$) | TC >75 cm ($n = 28$) |
|---|---|---|
| Gender male/female | 3/19 | 21/7* |
| Age (years) | 23 (23;25) | 24 (23;25) |
| BMI (kg/m$^2$) | 20.2 (19.6; 21.4) | 23.0 (22.2; 25.1)* |
| Thoracic circumference (cm) | 70 (68;73) | 82 (79;85)* |
| ALT (U/L) | 17 (13; 18) | 18 (14; 22) |
| GGT (U/L) | 16 (13; 20) | 18 (17;22) |
| LS S+ probe baseline | 4.6 (3.7; 5.2) | 5.3 (4.6; 5.6)* |
| IQR/median% S+ probe baseline | 16 (11; 17) | 16 (15;22)** |
| LS M+ probe baseline | 3.8 (3.3; 4.6) § | 4.6 (4.2; 5.3)* ** |
| IQR/median% M+ probe baseline | 16 (16;19) | 13 (11; 15) |
| CAP baseline | 185 (170;194) | 199 (172; 220) |
| CAP IQR | 35 (21; 42) | 40 (33; 45) |

*$P < 0.05$ *versus* TC below 75 cm.
**$P < 0.05$ *versus* S+-probe.
ALT, alanine-aminotransferase; CAP, controlled attenuation parameter; GGT, gamma-glutamyltransferase; IQR, interquartile range; LS, liver stiffness; TC, thoracic circumference.

## Discussion

Our study aids probe selection for Fibroscan in lean adults by showing that in adults with a TC below 75 cm, both the S+-probe and the M+-probe can be used based on the good agreement of the results and equal variances. LS results obtained with the S+-probe are about 15% higher irrespective of the TC, indicating a systematic error. This error is likely caused by the differences in probe characteristics (central US frequency, probe external diameter, peak-to-peak amplitude, and measurement depth). A comparable difference (approx. 10%) was found in healthy children who were assessed with the S+-probe and the M+-probe.[7] The clinical relevance of this error needs to be further evaluated and needs to be considered when interpreting the results. In addition, for lean adults with TC >75 cm, the S+-probe and the M+-probe measurements were also well comparable; however, the variance of the results was larger when using the S+-probe. This indicated that the S+-probe is not the optimal choice for individuals with a TC above 75 cm, in line with the manufacturer's recommendations. Interestingly, both the S+- and the M+-probes showed higher LS values in the TC >75 cm participants compared with the TC ≤75 cm participants. The TC >75 cm group was predominantly male and had a higher BMI, therefore, differences in body composition may be responsible for the observed difference in LS. In a recent meta-analysis of 16 082 apparently healthy individuals, it was shown that LS

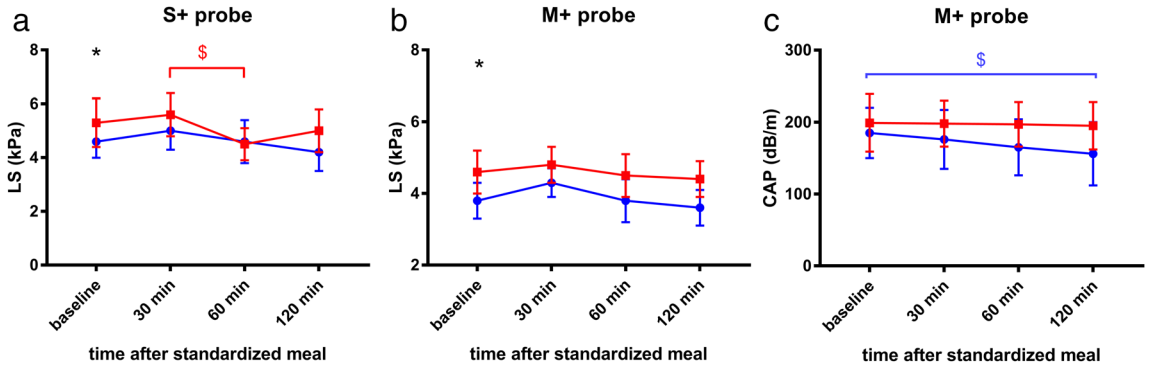


**Figure 1** (a) Liver stiffness (LS) measured with the S+ probe in participants with thoracic circumference (TC) ≤75 cm and TC >75 cm before and after a standardized meal. *Significant difference ($P < 0.05$) between TC groups, § significant difference ($P < 0.05$) between timepoint 30 and 60 min in the TC >75 cm group (red line). (b) LS measured with the M+ probe in participants with TC ≤75 cm and TC >75 cm before and after a standardized meal. *Significant difference between TC groups ($P < 0.05$). (c) Controlled attenuation parameter measurements with the M+-probe in participants with TC ≤75 cm and TC >75 cm before and after a standardized meal. §Significant difference between baseline and timepoint 120 min in participants with a TC ≤75 cm (blue line). —●—, TC ≤75 cm; —■—, TC >75 cm.

increased with increasing waist circumference, whereas male gender did not influence LS.[16]

Furthermore, we showed that a standardized light meal (300 kcal) equitable to a light breakfast did not cause an increase in LS measurements. This is not fully in accordance with previously published papers, where standardized liquid meals or normal food caused an increase in LS values in patients with chronic liver diseases.[8–11,13] Some studies used high-calorie meals with 600–1250 kcal, which may explain the difference in results.[11–13] Other studies however, used a liquid meal comparable with the one used in our study[8,9] and found an increase in LS in patients with different liver diseases irrespective of the degree of fibrosis. We cannot fully explain why in our hands, intake of a light standardized meal neither influenced the measurements with the S + - nor the M+-probe in healthy volunteers. CAP measurements decreased significantly 2 h after the meal, but only in the TC ≤75 cm group. This phenomenon was observed before: A faster and more pronounced CAP decrease than in our cohort was observed in a cohort of patients with chronic liver disease, who consumed 600 kcal. This reduction was attributed to reduced attenuation due to postprandial hyperemia.[12] Two subsequent studies found no influence of a meal on CAP measurements.[13,17] Our data suggest that a light meal does not immediately influence CAP measurements in lean adults, again suggesting that the intake of a light breakfast shortly before the examination may be possible.

In conclusion, the present study provides first data that in adults with a TC below 75 cm, the S+-probe in addition to the M +-probe of the Fibroscan device may be used and fasting may not be necessary. These data contribute to optimize the probe selection algorithm. However, the systematic error of +15% in LS measurements when using the S+-probe should be considered in the interpretation of the results. CAP measurements were technically possible with the M+-probe also in TC ≤75 cm patients. The finding that a light meal does not influence LS in lean adults, especially our novel findings using the S+-probe, may lift some of the burden of the examination for patients with eating disorders or also for pediatric patients, where withholding food may cause undue stress. It may also enhance the usability of Fibroscan devices during the day; however, further studies in different patient populations especially with different degrees of fibrosis are needed.

## References


1 EASL-EASD-EASO. Clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J. Hepatol.* 2016; **64**: 1388–402.

2 Ferraioli G, Filice C, Castera L *et al*. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 3: liver. *Ultrasound Med. Biol.* 2015; **41**: 1161–79.

3 Ferraioli G, Wong VW, Castera L *et al*. Liver ultrasound elastography: an update to the World Federation for Ultrasound in Medicine and Biology Guidelines and Recommendations. *Ultrasound Med. Biol.* 2018; **44**: 2419–40.

4 Sandrin L, Fourquet B, Hasquenoph JM *et al*. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med. Biol.* 2003; **29**: 1705–13.

5 Sasso M, Miette V, Sandrin L, Beaugrand M. The controlled attenuation parameter (CAP): a novel tool for the non-invasive evaluation of steatosis using Fibroscan. *Clin. Res. Hepatol. Gastroenterol.* 2012; **36**: 13–20.

6 Durango E, Dietrich C, Seitz HK *et al*. Direct comparison of the FibroScan XL and M probes for assessment of liver fibrosis in obese and nonobese patients. *Hepat. Med.* 2013; **5**: 43–52.

7 Goldschmidt I, Streckenbach C, Dingemann C *et al*. Application and limitations of transient liver elastography in children. *J. Pediatr. Gastroenterol. Nutr.* 2013; **57**: 109–13.

8 Alvarez D, Orozco F, Mella JM, Anders M, Antinucci F, Mastai R. Meal ingestion markedly increases liver stiffness suggesting the need for liver stiffness determination in fasting conditions. *Gastroenterologia y hepatologia.* 2015; **38**: 431–5.

9 Barone M, Iannone A, Brunetti ND *et al*. Liver stiffness and portal blood flow modifications induced by a liquid meal consumption: pathogenetic mechanisms and clinical relevance. *Scand. J. Gastroenterol.* 2015; **50**: 560–6.

10 Berzigotti A, De Gottardi A, Vukotic R *et al*. Effect of meal ingestion on liver stiffness in patients with cirrhosis and portal hypertension. *PloS one.* 2013; **8**: e58742.

11 Kjaergaard M, Thiele M, Jansen C *et al*. High risk of misinterpreting liver and spleen stiffness using 2D shear-wave and transient elastography after a moderate or high calorie meal. *PloS One.* 2017; **12**: e0173992.

12 Ratchatasettakul K, Rattanasiri S, Promson K, Sringam P, Sobhonslidsuk A. The inverse effect of meal intake on controlled attenuation parameter and liver stiffness as assessed by transient elastography. *BMC Gastroenterol.* 2017; **17**: 50.

13 Silva M, Costa Moreira P, Peixoto A *et al*. Effect of meal ingestion on liver stiffness and controlled attenuation parameter. *GE Port. J. Gastroenterol.* 2019; **26**: 99–104.

14 Mueller S, Sandrin L. Liver stiffness: a novel parameter for the diagnosis of liver disease. *Hepat. Med.* 2010; **2**: 49–67.

15 Shalimar KR, Rout G, Kumar R *et al*. Body mass index-based controlled attenuation parameter cut-offs for assessment of hepatic steatosis in non-alcoholic fatty liver disease. *Indian J Gastroenterol.* 2020; **39**: 32–41.

16 Bazerbachi F, Haffar S, Wang Z *et al*. Range of normal liver stiffness and factors associated with increased stiffness measurements in apparently healthy individuals. *Clin. Gastroenterol. Hepatol.* 2019; **17**: 54–64 e1.

17 Vuppalanchi R, Weber R, Russell S *et al*. Is fasting necessary for individuals with nonalcoholic fatty liver disease to undergo vibration-controlled transient elastography? *Am. J. Gastroenterol.* 2019; **114**: 995–7.