**Original Article**

**Comparison of computed tomography densitometry and shear wave elastography velocity measurements for evaluation of the liver volume in the nonalcoholic fatty liver disease**

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**Abstract:** Purpose: The aim of the present study is to evaluate and compare the values of velocities measured by the shear wave elastography (SWE), and those of the liver attenuation index (LAI) determined by the computerized tomography (CT) densitometry, in the nonalcoholic fatty liver disease (NAFLD). In other words, we aimed to compare the values of density measured by CT and the stiffness determined by elastography, in the liver steatosis. In addition, it is to investigate the effect of NAFLD on the liver volume. Materials and methods: Forty five cases with hepatosteatosis who had undergone abdominal CT and 50 individuals who did not exist with fatty liver clinically and radiologically, were investigated by ultrasonography (US) and SWE. The liver and spleen attenuation values were then measured in the images of non-contrast CT, and the LAI indices were calculated. Contrast images of abdomen were processed by the CT-Volume software and measurements of liver volume were performed using the interactive and automatic liver segmentation techniques together. Values of the liver volume, LAI, liver dimensions, and the shear wave velocities were determined and recorded in the patients with hepatosteatosis and controls; statistical comparisons were performed then. Results: In the nonalcoholic fatty liver, the mean value of velocity measured by SWE was found to be 1.08 (±0.11) m/s, and that of LAI measured by CT densitometry was 13.68 (±10.6). No correlation was observed between these two parameters (P>0.05). A high statistically significant difference between the patient and control groups in terms of the liver volume, LAI values and liver size has been observed (P<0.01). Direct correlations existed between the liver volume and LAI values, and the grades in US, and highly significant differences were determined (P<0.01). The mean values of the liver volume in the patient and control groups were determined to be 1917.4 (±425.9) cm$^3$ and 1311.4 (±241.4) cm$^3$, respectively. A high statistically significant difference between the groups in terms of liver volumes has been observed (P<0.01). Conclusion: In our study, we determined no correlation between the values of velocity measured by SWE, and the values of LAI measured by CT densitometry, in the NAFLD (P>0.05). This result indicates that there is no relation between the degree of stiffness evaluated by SWE, and the attenuation values measured by CT densitometry, in the non-alcoholic fatty liver. The liver volume was found to increase in NAFLD. We concluded that the CT densitometry can be used as an auxiliary technique associated with the US, in determining the degree of steatosis in NAFLD.

**Keywords:** Hepatosteatosis, shear wave elastography, computed tomography, liver attenuation index, liver volume

**Introduction**

Nonalcoholic fatty liver disease (NAFLD) is an important public health problem, the incidence of which increases with the increase in obesity problem. It is currently the most common chronic liver disease with high rates of morbidity and mortality both in the adults and children [1, 2]. NAFLD is associated with the infiltration of hepatocytes with fat, and includes the simple hepatic steatosis, nonalcoholic steatohepatitis, liver fibrosis, and liver cirrhosis; it may also cause hepatocellular carcinoma [3, 4]. Liver steatosis is defined as lipids’ constituting more than 5% of the liver weight, or fat vacuoles’ being observed in more than 5% of hepatocytes in the histological investigation [5, 6].

Liver biopsy and histological analyses are considered to be the reference standards of diag-
nosis in evaluating the fatty liver. The histological evaluation provides information concerning not only semi-quantitative evaluation, but also the degree of fibrosis. Since biopsy is an invasive procedure with high its costs and possible risks, it is an unrepeatable diagnostic test, which is not applicable enough. Furthermore, since lesions are not distributed equally in the liver parenchyma and sampling is inefficient during the liver biopsy, it may lead to inaccurate staging and faults in histological evaluation [1, 7].

Radiological findings play a significant role in the diagnosis of fatty liver, and the degree of fatness can be estimated by non-interventional methods such as ultrasonography (US), computerized tomography (CT), and magnetic resonance imaging [8]. Moreover, liver hardening (stiffness) is measured by many researchers in radiology and hepatology, using the non-invasive ultrasound elastography and magnetic resonance imaging [7]. CT is widely used in the quantitative and qualitative evaluations of hepatic steatosis [9, 10]. The degree of steatosis in the liver parenchyma is considered to be a non-invasive procedure, using CT densitometry. The evaluation of liver attenuation by non-contrast CT is one of the objective and non-invasive methods for the identification of asymptomatic hepatic steatosis [8]. The liver attenuation index (LAI) has been developed using the non-contrast CT, and this index has been used in many studies. The degree of hepatic steatosis can be determined by the LAI [9-11].

The shear wave ultrasound elastography (acoustic radiation force impulse) is a new technology that can be potentially applied in various fields, and also evaluates the stiffness of liver parenchyma. New application fields described for this imaging method have been progressively increasing in the literature [12]. Shear wave elastography (SWE) is a novel, future-promising and ultrasound-based diagnostic method, which ensures the evaluation of tissue stiffness by measuring the velocity of wave propagation [13-15]. SWE is applied by the ultrasound scanner using a conventional probe, without needing external compression, and thus decreasing dependence of an operator. In the literature, there are current studies that reveal the effectiveness of SWE as a diagnostic imaging method in the evaluation of diffuse and focal liver pathologies [16, 17]. SWE is recently used to evaluate fibrosis in the cirrhotic liver [7, 16]. The degree of liver fibrosis is the most important factor that determines the shear wave velocity (SWV). However, other factors may also affect the SWV [18]. Several non-invasive methods are used in evaluating the degree of fibrosis in order to avoid liver biopsy. The liver function tests and transient elastography are non-invasive, sensitive and accurate procedures in differentiating the cirrhotic and non-cirrhotic livers, and in evaluating the liver fibrosis. The accurate characterization and differential diagnosis are the most important aim of the current imaging modalities available [19].

The aim of the present study is to evaluate and compare the values of velocities measured by the SWE, and those of the LAI determined by the CT densitometry, in the NAFLD. In other words, we aimed to compare the values of density measured by CT and the stiffness determined by elastography, in the liver steatosis. In addition, it is to investigate the effect of NAFLD on the liver volume.

Materials and methods

Subjects

The images of the routinely applied abdominal CT in the patients over 18 years of age, obtained from various clinics determined between march 2015 and April 2015 at the Faculty of Medicine, Yuzuncu Yil University in the unit of Dursun Odabas Medical Center Radiology, were investigated retrospectively in our radiology station, using the qualitative and quantitative methods, and with regard to liver densities; the cases suspected of hepatosteatosis were invited to our clinic for the further investigations of B-mode US and SWE. The images of the previous abdominal CT in 45 cases with hepatosteatosis, and 50 cases without any sign of fatty liver clinically and radiologically, were reinvestigated, and these cases were reevaluated further. Ethics committee approval from the Ethic Committee of the Faculty of Medicine, Yuzuncu Yil University School of Medicine has been received (Date/Decision no: 02.03.2015/43). The values of body mass index (BMI) in all participants were primarily calculated, using the following formula: BMI = weight (kg)/height (m²). Demographic characteristics of the participants are illustrated in Table 1.

Exclusion criteria

The anamnoses and clinical courses of the cases were investigated, and those existing
with cardiac failure, disease of liver parenchyma, hepatic congestion, glycogen storage disease, hepatic cirrhosis, iron storage disease, and the cases below 18 years of age, or those undergoing chemo-radiotherapy, were excluded from the study. Moreover, we have not observed any liver pathology in the selected images of the abdominal CT.

**ARFI elastography**

The US and SWE investigations were performed using the Siemens ACUSON S2000TM (Siemens Healthcare, Erlangen, Germany), 4.0 MHz 6C1 HD convex probe. SWE was performed by the Virtual Touch Quantification option and in the morning at fasting state, on the mid-axillary line at the 8th-9th intercostal space, when the cases were in supine position, and their right arms were in hyperabduction. Following a mild inspiration and maintaining a brief breath-holding, a total of 10 measurements were performed from the right lobe of liver, and 2 cm to 5 cm deep from the liver capsule, using ROI devoid of the main vascular structures, and the mean values of SWV were calculated. In staging of hepatosteatosis in the patient group, we used the criteria of the US evaluation of diffuse hepatic steatosis.

**CT scanning**

CT was performed using a multi-detector row helical scanner (Somatom Emotion 16-slice; CT2012E-Siemens AG Berlin and München-Germany). Unenhanced and contrast-enhanced images were acquired during a single breath-hold. Scanning and reconstruction parameters for unenhanced images were 120 (Kv), 80-120 (Ef-Mass), 16 mm × 1.2 mm (Acquisition), 0.6 sec (Rotation time), 1, 2 mm (Slice collimation), 5.0-3.0 (Slice width), 0.80 (Pitch factor), 5.0 mm (Increment), section thickness, 5 mm; and reconstruction interval, 3 mm. Following the precontrast phase, multiphasic abdominal protocollas (biphasic or triphasic) examinations were performed by injection of 70-100 ml of non-ionic radiocontrast substance by means of injection systems.

Values of the liver and spleen Hounsfield units (HU) were measured in the images of non-contrast CT, in 1 to 3 different sections, and using sampling fields of 10 mm in diameter (Region of Interest; ROI), by the use of Syngo VE.52A software. The five different ROI determined for liver were located in the areas devoid of the main vascular structures. The mean of the HU values measured in these areas was calculated to determine the mean hepatic attenuation value. The three different ROI of 10 mm in diameter were located in the areas of spleen devoid of the main splenic vascular structures, in the same sections. The mean of the HU values measured from the ROI for spleen, were calculated, to determine the mean spleen attenuation. The LAI was calculated by subtracting the mean spleen attenuation value from the mean value of liver attenuation. The density of liver parenchyma is normally higher by 7-10 HU, than that of the spleen. By considering the degrees of hepatosteatosis determined by the LAI; cases with the values of LAI above five (5) were evaluated as normal, and those with values below five, were evaluated to exist with hepatosteatosis [20]. Contrast images of the patients, LAI values of whom were calculated, were transferred to the CT-Volume software (Siemens Syngo Multimodality Workplace; Version VE52A).

The external margins of the liver were drawn in each CT section, by a radiologist with a five-year experience of abdominal imaging, and by applying the interactive volumetric method. The mean number of sections in each case was found to be seven, and all of the remaining sections were stained automatically, by the program. The portal venous system, hepatic veins, inferior vena cava, and the gallbladder were not included. All individual sections were then controlled each, and the parts exceeding beyond, and deficient regions were designed properly with the liver contours, by the use of round erasers and widening tools; the total liver volume was thus obtained automatically.

The liver volumes and dimensions, LAI values, and SWVs in all of the 45 patients with hepatosteatosis, and control subjects were measured and recorded (Figures 1-4). And then, the statistical comparisons were performed.
Descriptive statistical values for the evaluated parameters were expressed as the mean, standard deviation, minimum, and maximum. The mean values of groups were compared using one-way variance analysis (one-way ANOVA). Relations between parameters in the groups were determined by Pearson correlation analysis. For discriminating the groups regarding

Figure 1. SWE, non-contrast CT images, and contrast CT MPR images. A 55-year old female case of the control group; LAI+13.2, the mean value of SWV 1.05 m/s, the liver volume 912.56 cm³, the liver size 13.2 cm.

Figure 2. US, SWE, non-contrast CT images, and contrast CT MPR images. A 50-year old male patient, existing with grade 1 hepatosteatosis; LAI-6, the mean value of SWV 0.96 m/s, the liver volume 1620.03 cm³, the liver size 14.7 cm.
these parameters, ROC curve analysis was performed to determine the cut-off values. The level of statistical significance was accepted as 5%. SPSS statistical software was used for the statistical analyses.

Results

In the non-alcoholic fatty liver, the mean value of velocity measured by SWE was found to be 1.08 (±0.11) m/s, and that of LAI measured by CT densitometry was 13.68 (±10.6). No correlation was observed between these two parameters (P>0.05).

The LAI levels evaluated by CT densitometry in the patient and control groups were to be -13.68 (±10.6) and +13.18 (±3.95), respectively. A high statistically significant difference was observed between these two groups (P<0.05).

Figure 3. US, SWE, non-contrast CT images, and contrast CT MPR images. A 33-year old female patient, existing with grade 2 hepatosteatosis; LAI-21, the mean value of SWV 0.90 m/s, the liver volume 1975.91 cm$^3$, the liver size 18.9 cm.

Figure 4. US, SWE, non-contrast CT images, and contrast CT MPR images. A 48-year old male patient, existing with grade 3 hepatosteatosis; LAI-30, the mean value of SWV 1.01 m/s, the liver volume 3018.14 cm$^3$, the liver size 19.2 cm.
The mean values of the liver volume in the patient and control groups were determined to be 1917.4 (±425.9) cm$^3$ and 1311.4 (±241.4) cm$^3$, respectively. A high statistically significant difference between the groups in terms of liver volumes has been observed (P<0.01).

The mean values of the liver size in the patient and control groups were found to be 18.83 (±2.19) cm, and 15.62 (±1.96) cm, respectively. A high statistically significant difference between the groups in terms of the values of liver size has been observed (P<0.01).

The mean SWV values in the patient and control groups were to be 1.08 (±0.11) m/s and 1.09 (±0.10) m/s, respectively (Figure 5). No statistically significant difference between the groups in terms of the mean values of velocity determined by SWE was observed (P>0.05).

The patients with hepatosteatosis were grouped as grade I, II, and III, using the US; the results of comparisons of these groups regarding the values of LAI, liver volume, liver size and SWV, are demonstrated in Table 2. A direct correlation was detected between the values of LAI and liver volume in each stage of the USG grade, which was significant statistically (P<0.01). A significant difference between the grade I and the grades II-III hepatosteatosis in terms of liver size has been observed, whereas no significant difference between the grade II and III has been observed (Figure 6). No statistically significant difference between the grades of steatosis and the values of SWV in US has been observed (P>0.05).

The relations between variances in the hepatosteatosis group were determined by the Pearson coefficient of correlation. The values

Table 2. The results of the one-way analyses of variance between USG grade and variances

<table>
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<th>N</th>
<th>Ort.</th>
<th>St. Sat.</th>
<th>Min.</th>
<th>Mak.</th>
<th>p value</th>
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<td></td>
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<td>Shear wave velocity (m/s)</td>
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<tr>
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<td>.91</td>
<td>1.36</td>
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</tbody>
</table>

between the groups in terms of LAI values was observed (P<0.01).

Figure 5. Box plot graphic in the control and hepatosteatosis (grade I-III) groups. In the shear wave elastography, the mean value of velocity does not differ significantly between the groups.
CT and shear wave elastography in fatty liver

Table 3. Pearson coefficients of correlation between the evaluated parameters in the group with hepatosteatosis

<table>
<thead>
<tr>
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<th>Volume</th>
<th>Size</th>
<th>Shear wave velocity</th>
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<tr>
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<td>Size</td>
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<td>Shear wave velocity</td>
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<td>.025</td>
<td>-.091</td>
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**: P<0.01.

The degree of steatosis is currently estimated by the non-interventional methods such as US, CT, and magnetic resonance imaging. The degree of steatosis in the liver parenchyma is evaluated non-invasively, by the CT densitometry [8, 9]. The evaluation of the hepatic steatosis by CT is based on the values of liver parenchyma attenuation. It is dependent on the composition of tissue, and was evaluated as HU. The value of fat attenuation is much lower than that of the soft tissue; therefore, hepatic steatosis lowers the liver parenchyma attenuation. There are various quantitative CT indices that have been used in the evaluation of hepatic steatosis. The two most frequently used indices are the absolute liver attenuation value (HU liver), and the difference between the liver and spleen attenuations (liver attenuation index) [21].

In a study conducted by Koenraad et al. and published in 2003, the liver density in the cases without fatty liver was found to be around 8 HU higher than that of the spleen [22]. The liver attenuation value shows a more strong relation with the histological degree of hepatic steatosis, when compared to the LAI. However, there may be false evaluations of the liver attenuation value due to the variabilities in
attenuation values determined with CT scanners produced by different companies [23, 24]. This error can be avoided by the use of LAI, which includes the spleen attenuation as an internal control [23]. In light of this knowledge, the liver attenuation indices have been developed by the use of non-contrast CT and the degree of hepatosteatosis can be determined by considering them. However, mathematical relations between the density and degree of histopathological steatosis have not been yet completely clarified in the literature; therefore, requirement of biopsy cannot be excluded in every case.

In the present study, we determined the LAI by CT, and the velocity values by SWE, and compared the results. We could not determine a statistically significant correlation between the values of LAI and SWV (P>0.05). This result indicates that in the NAFLD, there is no relation between the degree of stiffness measured by SWE, and the attenuation values measured by CT densitometry. Our study is the first in literature that compares the LAI values measured by CT densitometry, and the velocity values measured by SWE; thus, we consider that our results will contribute to the literature in this regard.

Bora et al. investigated the effect of non-alcoholic fatty liver on the liver volume, and in the control and patient groups, values of liver volume and LAI were determined to be 1315.24 cm³, 13.62 and 1743.62 cm³, -12.59, respectively. They revealed the quantitative data indicating that the liver volume and size increase correlated with the increase in degree of steatosis [10]. In our study, the LAI values evaluated by CT densitometry in the patient and control groups were found to be -13.68 (±10.6) and +13.18 (±3.95), respectively. A high statistically significant difference between the groups in terms of LAI values was observed (P<0.01). Moreover, a high statistically significant difference between the values of liver volume and US grades was observed (P<0.01). Our results related with the liver volume and LAI, are in accordance with those of the study carried out by Bora et al. Our study was conducted with a limited number of patients and control subjects, and the cut-off value for liver volume was found to be 1540.08 cm³. This may indicate a limited reference value for the unit of population that we studied. The result obtained from the volume measurements of our study reveals that there is a high negative linear correlation between the LAI and liver volume, and there is also a high statistically significant relationship between liver volume and steatosis as a result of the variance analysis when the statistically significant relationship between the LAI and US grade is considered. Studies conducted with greater numbers of patients and control subjects would reveal different results from ours. However, we consider that our study may provide an initial base profile in the short-term.

In our study, a high positive linear correlation between the increase in liver size and volume has been observed both in patient and control groups. In other words, a linear correlation exists between hepatomegaly and liver volume. In our study, the mean values of liver size and liver volume in the patient group were found to be 18.83 cm and 1917.4 cm³, respectively. These two values are above the cut-off levels. In the control group, the mean values of liver size and liver volume were found to be 15.62 cm and 1311.4 cm³, respectively. There is a high statistically significance between both groups in terms of the liver volume and size. (P<0.01). Results of variance analysis indicate that liver sizes, especially above 17.5 cm cause marked increases in the liver volumes. These results are in accordance with those of Bora and Lingurarun [10, 25]. In NAFLD, a positive linear correlation exists between the degree of steatosis, and liver size, which is highly significant statistically (P<0.01); however, liver size...
did not differ significantly between the grade 2 and grade 3 hepatosteatoses. In grade 2 and grade 3 hepatosteatoses, liver sizes were found to be similar; however, in grade 3, the liver volume was found to be significantly higher. This result reveals that the liver volume increases further in grade 3 hepatosteatosis, and the enlargement is not only in the kaudokraniel axis, but also in all axes. This fact has to be kept in mind during clinical evaluation. Hepatomegaly must not be expected in all cases with hepatosteatosis; however, in our study, a high negative linear correlation existed between the value of LAI, and liver size. Most of the cases with hepatosteatosis are asymptomatic; however, hepatomegaly is the most frequent sign of NAFLD [26]. In some studies, the rate of hepatomegaly is reported to be 75% in the liver steatosis [26-28]. Linguraru et al. determined marked increases in liver volumes, especially in the moderate and massive hepatomegalias when compared to normal population [25]. There are extremely rare studies in the literature that reveal numerical data related with hepatomegaly, and increase in liver volume, in the patients with hepatosteatosis. As far as we know from the literature review, this is the second study which reveals numerical data related with the increase in liver volume in NAFLD. The liver volume has currently been evaluated by three different measurement techniques, which are the manual, interactive, and automated types. In the present study, we used the interactive and automatic liver segmentation techniques together, in the measurement of liver volume.

In the cases with fatty liver, it is essential to determine the liver fibrosis by noninvasive evaluation, with the proper clinical management. It has been reported in a study that 5% of the cases with hepatosteatosis progress to NASH, and even to hepatic cirrhosis [29]. The SWE is a recently developed noninvasive method, which measures liver stiffness by using the internal mechanical excitation [7]. Many preliminary results have revealed the usefulness of this method in evaluating the liver fibrosis [7, 16].

In a meta-analysis study of D’Onofrio et al., they have reviewed all studies evaluating the values of SWV in the healthy individuals, and the cases with severe liver fibrosis; in this study, the mean values of velocity were reported to be 0.8-1.7 m/s (healthy subjects) and 1-3.4 m/s (cases with severe liver fibrosis), respectively [19]. In the study of Motosugi et al., SWV values in the cases with non-alcoholic fatty liver, and the healthy group without liver steatosis were found to be 1.02 (±0.12) m/s and 1.03 (±0.12) m/s, respectively; they obtained similar results in these groups. In light of these results, they reported that fat accumulation in the liver does not affect the liver stiffness, when measured by SWE [7]. In the study of Yoneda M et al., values of velocity determined by the SWE were found to be between 0.770 m/s to 2.990 m/s, in the cases with NAFLD; in this study, SWV values decreased gradually with the increase of grade in histological hepatic steatosis. In addition, SWV values in the cases with NAFLD and no fibrosis (simple steatosis, fibrosis grade 0) and the healthy volunteers were found to be 1.040 m/s and about 1.2 m/s, respectively. In light of these results, they determined that values of velocity were significantly lower in the group with NAFLD and no fibrosis, when compared to the group of healthy volunteers. As a hypothesis, they concluded that fat accumulation leads to a softer liver parenchyma [16]. In our study, SWV values in the patient and control groups were found to be 1.08 (±0.11) m/s and 1.09 (±0.10) m/s, respectively; the SWV values were similar in the groups, and a statistically significant difference did not exist (P>0.05). As a conclusion, we determined that fat accumulation in the liver does not affect the liver stiffness, when measured by SWE. The results of SWE in our study are similar to those of Motosugi et al., and they are in accordance with the literature. Moreover, we did not determine statistically significant correlations between the SWE results, and the degree of steatosis, LAI, liver volume, and liver size.

This study includes several limitations. The first limitation is the absence of pathological indicators of the fat accumulation. However, as mentioned above, degree of hepatic steatosis can be estimated by the LAI [30]; we consider that CT and US can be used together in the evaluation of fatty liver disease. Neglecting the possible existence of minimal fibrosis in the liver parenchyma, in the fatty liver, is the second limitation. In order to confirm the effect of fat accumulation in the liver on the measurement of liver stiffness; a more sensitive study is needed, that also includes the pathological
evaluations and confirmation. The third limitation is the limited numbers of patients and control subjects, which may cause a mild disadvantage. However there is an extremely limited number of studies in the literature, that reveal numerical data related with the increase in liver volume in NAFLD; our study is the first in literature that compares the results of CT densitometry, and the values of velocity measured by SWE, in the cases with NAFLD. The fourth limitation is the absence of consensus in the diagnosis of parenchymal changes by SWE in diffuse liver diseases that exist with steatosis and inflammatory changes, and also in demonstration of the effects of these changes on the SWV measurements [16, 31, 32].

Conclusion

In our study, we determined no correlation between the values of velocity measured by SWE, and the values of LAI measured by CT densitometry, in the NAFLD (P>0.05). This result indicates that there is no relation between the degree of stiffness evaluated by SWE, and the attenuation values measured by CT densitometry, in NAFLD. We showed the relationship between non-alcoholic fatty liver and liver volume, by statistical data. We concluded that a positive linear correlation exists between the liver size and liver volume in the NAFLD, and the liver volume increases in NAFLD. We determined that the CT densitometry can be used as an auxiliary technique associated with the US, in determining the degree of steatosis in NAFLD. Though the measurements of liver size were similar in grade 2 and grade 3 hepatosteatosis, we revealed a further increase in liver volume in the evaluation with CT, and we demonstrated that liver enlargement exists not only in the caudokranial axis, but also in the other axes; we determined a statistically significant increase in liver volume in grade 3. We obtained cut-off values for liver volume in grade 3. We performed SWE, we found out that hepatosteatosis does not affect the stiffness of liver parenchyma. These values obtained in limited numbers of patients and control cases, may indicate the reference values in the unit of population that we studied. Our results have to be supported by further studies conducted in larger series.

Ethical approval

Ethic Committee of the Faculty of Medicine, Yüzüncü Yıl University School of Medicine has been received (Date/Decision no: 02.03.2015/43).

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Informed consent was obtained from all individual participants included in the study.

Disclosure of conflict of interest

None.

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CT and shear wave elastography in fatty liver


