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The course and prognostic value of increased pancreas stiffness detected by ultrasound elastography during acute pancreatitis

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ABSTRACT

Background: In this study, we determined the pancreatic stiffness (PS) changes in the course of acute pancreatitis (AP) by ultrasound elastography and evaluated its relation with prognosis.
Material/methods: Pancreatic shear wave velocity measurements (SWM) were evaluated at the time of admission to the hospital, following clinical improvement, and one-month after for AP patients and compared to healthy volunteers. Its relationship with clinical severity indexes was evaluated.
Results: The pancreatic SWM value in the healthy group was 7.72 ± 2.50 kPa, and in AP group was 10.97 ± 2.26 kPa (p = 0.000). There was no difference between mild and severe pancreatitis. The mean SWM was 8.96 ± 1.53 kPa after disease remission, and 8.83 ± 1.24 kPa after 1-month.
Conclusions: PS increases significantly during AP and decreases with clinical improvement, but this was still higher than controls, and it kept its elevation after 1-month. We think that larger, long-term studies are needed to determine the clinicopathological significance of this.

1. Introduction

Acute Pancreatitis (AP) is characterized by inflammation of the pancreas. It is one of the most frequently encountered gastroenterological diseases; the incidence is equal in men and women, with a varying incidence between 4.9 and 73.4 cases per 100,000 [1–4]. AP is mildly edematous in 80–85% of the patients, and the pancreas returns to normal after a short time. However, it progresses seriously in 15–20% of patients, may lead to SIRS, and cause necrosis and mortality [5]. While mortality is 1.5% in mild AP, it can reach up to 17% in severe AP [6,7].

AP often heals without sequelae, but there is evidence that AP can progress to chronic pancreatitis (CP). However, little is known about the mechanisms of progression during the development of CP in ten percent of patients following the first AP attack and in 36% of patients with recurrent AP [8]. In recurrent acute pancreatitis (RAP), recurrent pancreatic inflammation may also be a prelude to the development of chronic pancreatitis [9,10]. It is difficult to predict transformation from RAP to chronic pancreatitis. A critical step in this progress is the development of pancreatic fibrosis, but there are other unknown factors.

Few studies investigating pancreatic stiffness during AP have shown an increase in pancreatic stiffness [11–15]. However, its relationship with the course and prognosis of AP has not been adequately evaluated and its natural course is unknown.

In this study, we tried to determine the natural history of pancreatic stiffness by ultrasound two-dimensional shear-wave elastography (2D-SWE) at hospitalization with the diagnosis of AP, when clinically complete recovery and 1 month after discharge. In addition, we examined the relationship between the change in pancreatic stiffness and the prognosis and severity of AP.

2. Material-method

This is a prospective, cross-sectional study carried out in a tertiary care academic medical centre between November 2019 and January 2021. All consecutive patients over 18 years of age who were hospitalized in our clinic with a diagnosis of AP were included in the study. Pancreatic stiffness of patients with AP and healthy control group was evaluated by 2D SW ultrasound elastography. Demographic features, clinical, laboratory and radiological data; AP etiology, length of hospital stay (days), presence of organ failure, local and systemic complications, interventions, and death were recorded for all patients. AP type, organ failure, and local complications were defined according to the Revised Atlanta Classification [17]. The study was planned in accordance with the Helsinki

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Declaration of ethics and was approved by the Ethics Committee of our University (Date:6/2/2019, Number: 2019/65). Informed consent forms were obtained from the patients and those who agreed to participate in the study were included in the study. Control group was made up of completely healthy individuals. AP diagnosis was made by the presence of at least two of the following 3 criteria: 1) Abdominal pain 2) serum amylase and/or lipase greater than three times the upper limit of normal 3) morphological changes of the pancreas on abdominal imaging (Transabdominal Ultrasonography (TAU), Contrast Enhanced Computed Tomography or Magnetic Resonance Imaging of the abdomen) [1]. Patients with chronic pancreatitis, malignancy, chronic liver disease, ascites, solid or cystic pancreatic mass, pregnant or a history of pancreatitis, and those with difficult visualization of the pancreas on B-mode sonography were excluded. Biochemical tests and blood count were recorded. The patients were evaluated in terms of mild and severe pancreatitis. Atlanta, Ranson, APACHE 2 scores of AP patients were calculated. TAU and elastography for AP patients and control group were performed at the admission. When the patients' clinical findings and serum amylase and lipase levels returned to normal, TAU and elastography examinations were repeated before discharge and 1 month after discharge with the same principles.

2.1. Ultrasonographic examination

The transabdominal ultrasonographic examinations were performed using a high-resolution ultrasonography machine (Toshiba Applio 500, Tokyo, Japan) with 1–6 MHz convex transducer. To avoid the inter-observer variability, the ultrasonography in this work was performed by a single gastroenterologist with 8 years of experience. At first, patients underwent conventional B-mode ultrasound examinations in the supine position. All detailed TAU assessment was performed. Then, assessment of the pancreatic parenchyma in all three segments was achieved: head, body, and tail and the pancreatic location; size, ecogenic appearances, shape, the pancreatic duct, boundaries, and peripancreatic areas were evaluated. Pancreatic and peripancreatic fluid collection was assessed. In case of the occurrence of inadequate visualization of the pancreatic tail in the epigastric area in transverse plane, patients were screened using the spleen as an acoustic window in the left lateral plane. B-mode US was also performed to detect possible gallbladder and common bile duct stones.

2.2. 2D shear wave elastography evaluation

SWE was performed after the B-mode US. During the SWE examination, elastographic images of the pancreas were obtained during a very light contact with the skin of the US probe. During ultrasonographic examination, patients were asked to hold their breath, and after image stabilization, without obvious motion artifact, the pancreas was clearly visualized. This maneuver precludes movement artifacts, as possible. Then, the region of interest (ROI) window with the dimensions of 10 × 10 mm was placed on the pancreatic tissue, on the ultrasonography monitor, without contact with the liver parenchyma, adjacent vessels, or structures of the digestive tract. After positioning the ROI window, a shear wave elastography impulse was triggered. After a short while, (about 1–2 s), pancreatic stiffness (kPa) was displayed, along with the depth of the ROI placement. Five elastographic images of the pancreas were taken, and the median of the five measurements was used as the valid value. We used transverse or slightly oblique transverse sections [18–20].

3. Results

Eighty-one patients with AP and 74 healthy control persons were evaluated. When the AP group and the control group were compared, according to age (52.3 ± 17.2 year vs 51.2 ± 16.3 year, p = 0.671), gender (p = 0.563), and BMI (27.62 ± 4.05 kg/m^2 vs 28.05 ± 5.00 kg/m^2, p = 0.760), there was no difference in between (Table 1). AP was found to be mild in 52 patients and severe in 29 patients. Significant differences between these two groups were found only in age (48.34 ± 15.94 year vs 60.67 ± 16.88 year, p: 0.002) and frequency of peripancreatic fluid (3 vs 6, p: 0.043). AP was not mortal in any patient (Table 2).

The mean pancreatic shear wave velocity measurements (SWM) value of AP patients during admission was 10.97 ± 2.26 kPa, and that of the control group was 7.72 ± 2.50 kPa. There was a significant difference between the two groups (p = 0.000) (Table 1) (Fig. 1). When categorized according to Atlanta criteria, pancreas SWM was 9.05 ± 1.44 kPa in mild AP, and 8.61 ± 1.72 kPa in severe AP (p: 0.236). According to Ranson and APACHE 2, there was no difference between mild and severe AP in pancreatic SWM (Table 3).

In the AP group, after clinical improvement, the mean of pancreatic SWM value was 8.90 ± 1.54 kPa and it showed a significant decrease compared to the value on admission (p = 0.000) (Fig. 1). Although there was a significant improvement, still these results were statistically significantly higher than pancreatic SWM values of the control group (8.90 ± 1.54 kPa vs 7.72 ± 2.50 kPa, p = 0.000) (Fig. 1).

Pancreas elastography was performed in 24 patients one month after clinical improvement; the mean pancreatic SWM value was found to be 8.84 ± 1.24 kPa. There was no difference between the SWM after clinical improvement and the SWM one month later (8.96 ± 1.53 and 8.83 ± 1.24, respectively, p = 0.315) (Table 4, Fig. 1). Evaluation of these patients within the whole AP group and separately; the first (11.35 ± 1.79 kPa), after clinical recovery (8.96 ± 1.53 kPa), and one month later measurement results (8.84 ± 1, 24 kPa) were all similar. Fifteen of these patients had mild and 9 had severe AP. In addition, there was no significant pancreatic SWM difference between the groups according to the Atlanta Classification for severity of AP (p = 0.194) (Table 4). Of these patients, 13 were female, 11 were male.

According to the Spearman's test, there was no correlation between mean pancreatic SWM value and hospitalization period and biochemical parameters FPG, CRP, Urea, Creatinine, ALP, GGT, LDH (p = 0.597, 0.286, 0.084, 0.459, 0.790, 0.445, 0.922, 0.650, respectively).

4. Discussion

AP, is an acute inflammatory disease of the pancreas with infiltration by granulo-lymphocytic cells and disseminated necrosis of acinus cells and interstitial edema. AP leads either mild or severe pancreatic inflammation, which are characterized pathologically by edematous interstitial tissue and hemorrhage, respectively, with an inflammatory response as a result of the former and parenchymal necrosis as a result of the latter. These histopathological changes in AP affect pancreatic elasticity. Elastography, which is a pioneer imaging method in the detection of organ stiffness, is used for this purpose in the pancreas, beside various tissues. Although histopathological evaluation is definitive evidence for the presence of inflammation or fibrosis and, to determine the cause of the pancreatic stiffness, histological examination requires a biopsy, however, this invasive procedure is not always possible in daily practice. Even if a tissue sample is taken, there may also be grading errors due to the uneven distribution of pancreatic inflammation or

Table 1
Comparison between the AP group and control group.

	AP group (n = 81)	Control group (n = 74)	p
Age (years)	52.39 ± 17.28	51.24 ± 16.35	0.671
Gender (M/F)	35/46	32/42	0.563
BMI (kg/m^2)	27.62 ± 4.05	28.05 ± 5.00	0.760
Hospitalization time (days)	4.86 ± 3.01	NA	–
WBC (×1000/mm^3)	11.83 ± 5.71	7.18 ± 2.15	0.000
FPG (mg/dl)	140.52 ± 64.71	99.2 ± 20.49	0.000
Urea (mg/dl)	33.58 ± 22.05	28.41 ± 10.17	0.085
Creatinine (mg/dl)	0.8 ± 0.42	0.72 ± 0.24	0.190
AST (U/L)	162.23 ± 193.65	25.87 ± 19.28	0.000
ALT(U/L)	192.13 ± 406.63	27.12 ± 29.23	0.001
ALP(U/L)	143.14 ± 114.34	67.12 ± 34.34	0.000
LDH(U/L)	326.09 ± 130.26	176.58 ± 48.63	0.000
CRP (mg/L)	61.57 ± 87.07	4.47 ± 8.16	0.000
Pancreas SWM (kPa)	10.97 ± 2.26	7.72 ± 2.50	0.000

Table 2
Comparison of mild and severe AP patients on admission to hospital.

	Atlanta 2 mild (n = 52)	Atlanta 2 severe (n = 29)	p
Age (years)	48.34 ± 15.94	60.67 ± 16.88	0.002
Gender (M/F)	19/33	16/13	0.175
BMI (kg/m^2)	28,10 ± 5,28	27,97 ± 4,50	0.914
Etiology (biliary/non-biliary)	34/18	18/11	0.182
Mean hospitalization time (day)	4,42 ± 2,47	5,65 ± 3,72	0.118
Mean Pancreas SWM (on admission)	9,05 ± 1,44	8,61 ± 1,72	0.236
Peripancreatic fluid collection	3/52	6/29	0.043
FPG (mg/dl)	141.9 ± 70,59	138.16 ± 54,3	0.810
Urea (mg/dl)	32.51 ± 25,12	35.61 ± 14,87	0.566
Creatinine (mg/dl)	0.77 ± 0.42	0.85 ± 0.44	0.421
AST (U/L)	139.15 ± 160.09	204.1 ± 240.90	0.163
ALT(U/L)	188.90 ± 478.87	197.98 ± 231.39	0.926
ALP(U/L)	128.28 ± 101.74	169.58 ± 131.76	0.134
GGT(U/L)	182.18 ± 189.96	231.69 ± 249.27	0.342
LDH(U/L)	319.78 ± 122.56	337.5 ± 144.98	0.581
Total Bilirubin (mg/dl)	1.52 ± 1.91	1.55 ± 1.53	0.947
Direct Bilirubin (mg/dl)	0.67 ± 1.18	0.76 ± 1.12	0.724
CRP (mg/L)	54.24 ± 77.00	74.12 ± 102.38	0.340
WBC (×1000/mm^3)	12.46 ± 6.1	10.74 ± 4.88	0.205

fibrosis.

Elastography is an ultrasound imaging modality, and the concept of elastography was first proposed in 1991 by Ophir et al. [21]. It has been used for assessing the tissue stiffness. The stiffness of an individual organ can be estimated via tissue biomechanical response to compression, during elastographic assessment [22]. The procedure can be executed by two modalities: strain elastography and shear wave elastography (SWE). The tissue displacement is used for strain elastography caused by tissue compression which is produced mechanically by the investigator, using the probe. As a qualitative technique, it is mostly operator dependent. In SWE, the source of the impulse which cause tissue compression is focused ultrasound waves: acoustic radiation force impulse (ARFI). In this modality, the speed of the laterally moving shear waves in the target tissue is used for prediction of organ stiffness; the speed of the wave is direct proportional to the tissue stiffness [18]. The measurement unit for SWE is either meters/second (m/s), or kilopascal (kPa) [11–16,18–20]. There are several methods for performing SWE: 2D-SWE, point SWE, transient elastography (TE), single shot (VTIQ), and real-time (SSI technology). Various elastography methods seem to be comparable [23–28]. SWE can be easily applied for pancreas because theoretically ARFI can be emitted to wherever desired in the entire pancreas [20,29–31].

Being overweight as in our patient and control group or ileus that may develop during the course of AP may cause the concern that ultrasonographic evaluation of the pancreas may be difficult or unreliable. However, there are many publications in the literature, concluded that SWE has been shown to be clinically useful in the evaluation of pancreatic diseases such as acute [11–16] or chronic pancreatitis and pancreas masses [32–42], and pancreatic steatosis [20]. In our large-scale population survey, we found that 35% of the Turkish population was overweight and 45% obese, and we were able to evaluate the pancreas almost completely ultrasonographically in the same population [43,44]. Of course, there were no AP patients in this group, but results from previous studies involving AP patients showed that TAU and SWE can be safely and effectively performed in AP patients. Similarly, in our study in which pancreatic steatosis was evaluated with ultrasound SWE, ultrasonographic evaluation could be performed effectively in overweight and obese patients [20]. There was no ileus in our patient group with AP. Thus, we did not have any concern about the effectiveness and reliability of TAU and SWE in our study.

There are several elastography studies in the literature investigating how these histopathological changes in AP affect pancreatic elasticity. While some of these studies showed increased pancreatic stiffness, there were also those who showed no change. But most of them looked for an elastographic cut off value that would be valuable in the diagnosis of AP. First of all, Maaten et al. reported that the mean SWM value of normal peripancretic soft tissue was 1 m/s. They have suggested that determination of the mean SWM value of peripancretic soft tissue above 2.2 m/s suggests AP. They also have reported the mean SWM values are 1.28 m/s, 1.25 m/s,

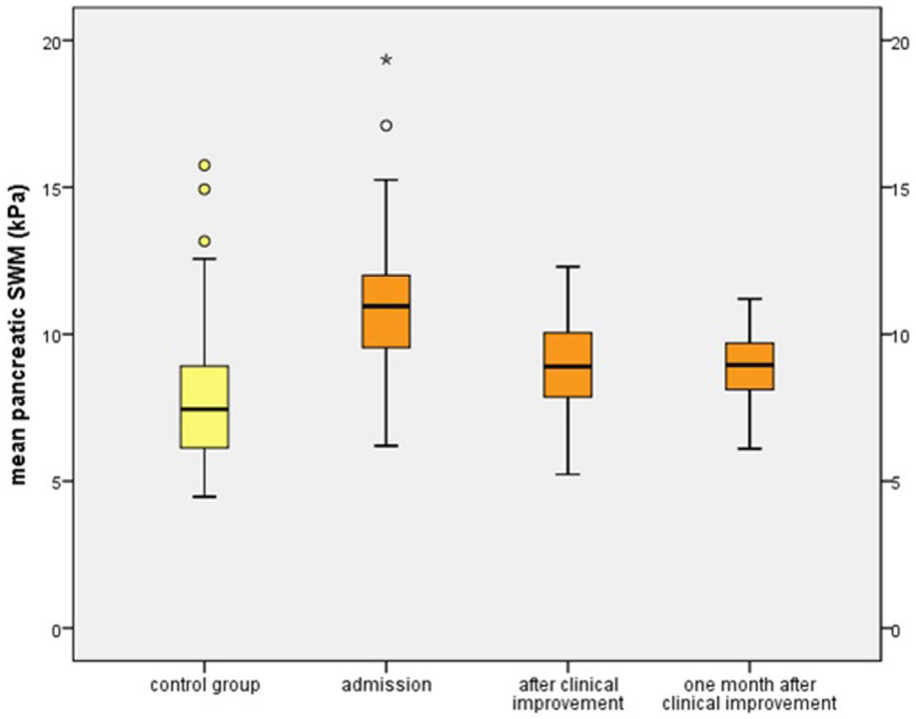

Fig. 1. Comparison of pancreatic SWM in control group and AP patients (at admission, after clinical improvement, and one month after clinical improvement).

Table 3
Pancreatic SWM comparisons according to Ranson and APACHE 2 scores.

	Score	Pancreas SWM (kPa)	p
Ranson	<3	9.00 ± 1.54	0.176
	≥3	8.39 ± 1.53	
APACHE 2	<8	8.99 ± 1.47	0.395
	≥8	8.68 ± 1.68	

and 3.28 m/s in normal pancreas, chronic pancreatitis and acute pancreatitis, respectively [11]. Later, Göya et al. reported that SWM separated AP from normal parenchyma with 100% sensitivity and 98% specificity when the cut-off value was determined as 1.63 m/s (at the time of first admission to the hospital) [12]. In this study, necrotic tissue detected by CT in 6 patients and VTQ values obtained by elastography ranged from 0.5 to 1.2 m/s. Lower SWM values were obtained with Virtual Touch imaging elastograms of necrotic areas (tissue losses) showed lower stiffness than non-necrotic pancreatic tissue [12]. Durmaz et al. reported statistically significant difference by comparing mean SWM values 23.77 ± 6.72 kPa in asymptomatic volunteers and 45.71 ± 10.72 kPa in patients with AP ($p < 0.001$, $t = -3.685$). According to this study, AP can be diagnosed with a sensitivity and specificity of 98.0% when 29.45 kPa was determined as cut-off value and with a 96.0% sensitivity and 98.3% specificity when 2.77 m/s was determined as the cut-off value. They have suggested that SWM can be used as an effective imaging method with high sensitivity and specificity in diagnosis of AP. The SWM values reported in this study were very high and the authors attributed this high values to their calculate model using the average SWM values obtained by drawing the whole of the pancreas head and body parts with the free ROI [13]. Kaya et al. reported mean SWM was significantly higher in the AP patient group than in the control group (2.43 ± 0.08 vs. 1.27 ± 0.025 m/s, $p < 0.001$); they designed SWM cut-off value of 1.63 m/s was associated with 100% sensitivity and 98% specificity for the diagnosis of AP [14]. Goertz et al. showed higher shear wave velocities in pancreatic lipomatosis, acute pancreatitis, chronic pancreatitis and adenocarcinoma compared with healthy parenchyma [15]. In another study, Xie et al. showed no significant difference in SWM values that were obtained from two groups one consisted from patients with AP and one from asymptomatic controls. In the healthy control group, the mean SWM value obtained from the pancreatic head and body were 1.18 ± 0.23 m/s, and 1.21 ± 0.20 m/s, respectively. In patients with AP, the mean SWM obtained from the pancreatic head and body were 1.18 ± 0.20 m/s, and 1.25 ± 0.19 m/s, respectively, and there was no statistically significant difference between the part of the pancreas [16].

We found that the mean pancreatic SWM value was significantly higher than healthy controls during AP attack. Although there was a significant decrease in this value with the clinical improvement, it was still higher than the healthy control values. In most of the studies in the literature, it was found that pancreatic stiffness increased during AP, and the effectiveness of a cut-off value in the diagnosis of AP was also shown. However, in our opinion, the main problem is the increase in pancreatic stiffness during AP and how it evolved and whether it is related to prognosis. Because, AP

Table 4
Pancreatic SWM comparisons of patients after clinical remission and one month after clinical remission, according to the Atlanta Classification.

	Atlanta mild (n = 15)	Atlanta severe (n = 9)	Total (n = 24)
Pancreatic SWM (kPa) after clinical improvement	9.33 ± 1.25	8.36 ± 1.81	8.96 ± 1.53
Pancreatic SWM (kPa) one month after clinical improvement	9.07 ± 0.97	8.44 ± 1.58	8.83 ± 1.24

diagnosis can usually be made easily; symptoms and signs, elevated serum amylase, lipase level, and/or radiological findings are relatively easy to confirm in most of patients. Of course, some patients have subtle clinical or laboratory findings and it may be difficult to diagnose AP. Therefore, the pancreatic SWM value detected in this group of patients can be really useful in diagnosing AP. However, another important problem is that, it is difficult to predict the clinical course and the probability of complications in patients with AP, on admission. AP has a variable clinical course. Complete recovery without permanent organ dysfunction occurs in most of patients with AP. However, the mortality rate in the patients with infected necrosis can reach up to 30% [6,45]. Patients with uncomplicated edematous AP can be treated in local hospitals, whereas the patients with complicated necrotizing AP need to be treated experienced reference centers. Also, most of AP patients have mild and self-limited disease and recover without sequelae, but 10% can progress to chronic pancreatitis. Various laboratory and clinical predictive markers are used for early prediction of clinical course, local and systemic complications, and prognosis, and consequently, various scoring systems have been developed [46,47]. However, they are not sensitive enough, they are complex, expensive, and some cannot be used in the early stages of the disease or are not available in all hospitals. Currently, evaluation systems are being developed in AP to predict prognosis and clinical severity. In two of the elastography studies performed in AP, the relationship between the change in pancreatic stiffness and prognosis and clinical course was evaluated. Durmaz et al., in their study, found that SWM value has no predictive value for the development of necrosis, local and systemic complications, and mortality in AP; and no correlation was found between SWM (either m/s or kPa) and the Ranson score, also no correlation was found between SWM (m/s) and CT severity index (CTSI). However, they have showed significant correlation between kPa and CTSI; therefore, they concluded that it is possible to use the kPa values together with SWM in evaluating the severity of AP [13]. Similarly, Kaya et al. reported no significant difference in mean SWM value between the patients with and without complications and between the patients with edematous and necrotizing AP. There was also no correlation between mean SWM value and age, mean length of hospital stay, and mean amylase level. They concluded that it has no value for the prediction of clinical course of AP [14]. We did not find a relationship between pancreatic SWM values, and clinical and laboratory findings, age, gender, and length of hospital stay, at the time of the diagnosis of AP and after clinical improvement. However, in our study, unlike the others, we found that the pancreatic SWM value was still at a similar level to the pre-discharge value and still higher than the healthy controls, although the clinical improvement was completely recovered one month after discharge. Although, unfortunately, we were able to make this assessment in 30% of AP patients, we think that these results allow us to evaluate the course of pancreatic stiffness after AP recovery. This was not related to the mild or severe past of AP. Although a definite conclusion cannot be reached with this result obtained from our study, the fact that the pancreatic SWM value that increased during AP does not return to normal one month after discharge may indicate a permanent or long-term deterioration in pancreatic tissue elasticity. In a recent study, it has been shown that Recurrent AP increases pancreatic stiffness [48]. There was a significant difference in shear wave velocity (SWV) between patients (1.27 ± 0.50 m/s) and controls (1.00 ± 0.17 m/s) (p-0.001). There was a positive correlation between SWV and number of pain episodes (p-0.026). The stiffness increases with the number of episodes of pancreatitis. They suggested that the increased SWM values in RAP indicate the hardening of the pancreas, and that RAP may progress to chronic pancreatitis. Approximately one third of patients with RAP may progress to chronic pancreatitis [8,10].

In conclusion, we showed that pancreatic stiffness increases significantly during AP and then decreases significantly with clinical improvement, but this decreased value was still higher than controls, and it kept its height after 1 month. We think that long-term studies in larger cohorts are needed to determine what these changes mean.

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