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ORIGINAL ARTICLE

Male Health

Quantitative assessment of the aging corpus cavernosum by shear wave elastography

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We wanted to determine whether shear wave elastography (SWE) could be used to evaluate the aging degree of the corpus cavernosum (CC) and to identify the histological basis of changes in SWE measurements during the aging process. We performed a cross-sectional study enrolling healthy participants of different ages. We measured the Young's modulus (YM) of the penile CCs by SWE and assessed erectile function using the International Index of Erectile Function-5 (IIEF-5). Histological investigation was performed in surgically resected penile specimens from a separate group of patients to examine the smooth muscle and collagen content of the CCs. Furthermore, we measured the YM, erectile function, smooth muscle, and collagen content of the CCs in different age groups of rats. Finally, we enrolled 210 male volunteers in this study. The YM of the CC (CCYM) was positively correlated with age ($r = 0.949$, $P < 0.01$) and negatively correlated with erectile function ($r = –0.843$, $P < 0.01$). Histological examinations showed that CCs had increased collagen content but decreased smooth muscle content with increased age. The same positive correlation between CCYM and age was also observed in the animal study. In addition, the animal study showed that older rats, with increased CCYM and decreased erectile function, had lower smooth muscle content and higher collagen content. SWE can noninvasively and quantitatively evaluate the aging degree of the CC. Increased collagen content and decreased smooth muscle content might be the histological basis for the effect of aging on the CC and the increase in its YM.

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INTRODUCTION

Erectile dysfunction (ED) is one of the most common sexual dysfunctions in men. Its incidence increases significantly with age.[1–3] Various causes can result in ED in elderly men, especially those who have chronic illnesses, such as cardiovascular, endocrine, and metabolic diseases. All these chronic illnesses can contribute to the development of ED.[4,5] Furthermore, age itself has been demonstrated as an independent and primary risk factor for ED.[6,7]

The corpus cavernosum (CC), two cylinders of tissue in the penile shaft, are the most important structures for erectile function. Similar to other organs and tissues in the human body, the CCs undergo natural aging. The aging of the CCs will theoretically cause a decline in erectile function.[8–10] However, there are limited studies on the aging process of the CCs, probably due to the difficulty of obtaining study materials and the lack of standard criteria to evaluate the degree of aging of the CCs. Thus, a noninvasive and objective method to assess the degree of CC aging is required.

Shear wave elastography (SWE) is a new type of ultrasound examination that can provide noninvasive and quantitative assessments of tissue structures. SWE is an ultrasound technology that generates transverse shear waves in the target tissue by ultrasonic pulses. These waves are detected by the transducer, and their speed is used to calculate the Young's modulus (YM) of the tissue, which is directly related to its stiffness.[11–18] Our hypothesis is that SWE will be able to assess the degree of aging of the CCs. In the current study, we measured the YM of the CC (CCYM) by SWE in men in different age groups and explored the histological changes in the CC with aging. The CCYM and the structural changes in different age groups of rats were also measured and compared. We aimed to determine whether SWE could be effective as a noninvasive and quantitative method to assess the degree of CC aging.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China; approval No. XJTU1AF2019LSL-047) with a clinical registration number of ChiCTR2000029370. The animal study was approved by the Committee on the Ethics of Animal Experiments of Xi'an Jiaotong University (approval No. XJTU2020-579). All studies were performed in accordance with the Declaration of Helsinki.

Participant enrollment and group assignment

Healthy male volunteers who had undergone a routine physical examination at the health examination center of the First Affiliated Hospital of Xi'an Jiaotong University were enrolled through recruitment advertisements. Volunteers with chronic diseases (diabetes, hypertension, and cardiovascular disease) or other significant abnormal findings that might affect erectile function were excluded. Then, the volunteers willing to participate in this study signed informed

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consent before undergoing SWE examinations. For each child involved in the study, a guardian signed informed consent (with the agreement of the child). The subjects in the study were grouped by age: 5–10 years old, 20–29 years old, 30–39 years old, 40–49 years old, 50–59 years old, 60–69 years old, and ≥70 years old, with 30 cases in each group. An International Index of Erectile Function-5 (IIEF-5) value was recorded for participants aged 20 years and older to evaluate erectile function.

SWE examination

SWE examination was performed as described previously.[11–18] Briefly, an Aixplorer ultrasonic system (Aixplorer Supersonic Imagine, Aix-en-Provence, France) with a Superlinear SL15-4 probe (frequency range of 7.5–15 MHz; mechanical index [MI]: 1.5; thermal index of soft tissue [TIS]: 1.2) was utilized. The participants were positioned supine on the examination bed. Each participant held the dorsal side of his penis against the abdominal wall using his index finger, with as little pressure as possible on the penis. The examiner gently placed the probe on the ventral side of the penis and used the two-dimensional ultrasonography mode to scan the entire penis and show the structural organization of the CCs. After freeze-frame images were taken, the contact area between the probe and the ventral surface of the penis was filled with gel, and the pressure on the penis from the probe's weight and the examiner's hand was minimized. The ultrasound was then switched to SWE imaging mode and set to measure the YM in kilopascals (kPa). The image was optimized and adjusted to a standard setting (*e.g.*, frequency range of 7.5–15 MHz; MI: 1.5; TIS: 1.2). The CCs were displayed in transverse and longitudinal views. Three images of the bilateral CC tissues were obtained in real time. For the animal study, the rats underwent SWE examination of the penis under anesthesia; the rats were positioned supine on the examination bed, the dorsal side of the penis was gently pushed against the abdomen with the probe, and SWE examination was then performed as described above. All SWE examinations were performed by the same doctor, and each SWE was repeated three times.

Histological study in resected human penile specimens

Paraffin-embedded penis specimens from the First Affiliated Hospital of Xi'an Jiaotong University from January 2010 to December 2020 were collected. All specimens had been resected from patients with penile squamous cell cancers and included the tumor as well as adjacent normal penile tissues. The normal tissue within approximately 2 cm of the tumor margin were stained with hematoxylin and eosin (H&E) and Masson's trichrome (Baso Diagnostics Inc., Zhuhai, China). An experienced pathologist reviewed all slides to exclude tumor tissue. Image-Pro Plus 6.0 image analysis software (Media Cybernetics, Rockville, MD, USA) was used to measure the smooth muscle and collagen content of the CCs.

YM and histological changes in the rat CC in different age groups

Since it is difficult to obtain CC samples from healthy humans, we performed an animal study to measure YM and evaluate the histological changes in the CCs of rats at different ages. Thirty-six male Sprague–Dawley (SD) rats were obtained from the animal center of Xi'an Jiaotong University and were randomly divided into three groups with 12 rats in each group. The animals were maintained on 12-h/12-h light/dark cycles with free access to food and water before the experimental procedures.[19] SWE measurements of the CCs were performed under anesthesia at ages of 3 months, 12 months, and 24 months; erectile function was assessed by determining maximum intracavernous pressure (ICP)/mean arterial pressure (MAP) 1 day after SWE examination. Briefly, anesthesia was induced with isoflurane (RWD Life Science, Shenzhen, China), and the left carotid artery was carefully exposed and cannulated with heparinized (200 IU ml^{-1}) venipuncture catheter (26 gauge; Closed IV Catheter System, Becton Dickinson Medical Devices Co., Ltd., Franklin Lakes, NJ, USA) connected to a pressure transducer to measure arterial pressure. A low midline abdominal incision was made, and the left cavernous nerve was carefully exposed and isolated. After the penis was denuded of skin, a heparinized (200 IU ml^{-1}) 24-gauge needle (SGJS Medical Equipment Group Co., Ltd., Luohe, China) connected to a BL420 biofunction experiment system (Chengdu TME Technology Co., Ltd., Chengdu, China) was inserted into the penile crus to record the ICP. The cavernous nerve was electrically stimulated at a voltage of 5 V, a frequency of 20 Hz, and a pulse width of 5 ms for a duration of 60 s. The maximum ICP and arterial pressure were recorded simultaneously, and the ratio of ICP to MAP was also calculated.[7] Rats were sacrificed by exsanguination under deep anesthesia; afterward, the penis of each rat was harvested and fixed, and the middle part of the penis was stained with Masson's trichrome. The collagen and smooth muscle content of the CC were measured.

Statistical analyses

Statistical analysis was performed in SPSS version 22.0 (IBM, Chicago, IL, USA). Continuous variables were tested for normality of distribution with the Kolmogorov–Smirnov test and are presented as the mean ± standard deviation (s.d.). The Kruskal–Wallis H-test was used to compare the SWE scans of the CCs among different age groups, between the left and right CC in the transverse section, and between the left and right CC in the longitudinal section. The Games–Howell test was used for pairwise comparisons. For comparisons among groups, one-way analysis of variance followed by a *post hoc* Bonferroni test was applied. Correlations were evaluated by the Spearman correlation test. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of study participants

We enrolled 210 male volunteers in the study. **Table 1** shows the YM of the CC in different age groups. As in previous studies,[11–14] there was no significant difference in the YM between the left and right CCs or between the transverse and longitudinal views. Therefore, the YM of the longitudinal view of the left CC was used in this study.

YM was positively correlated with aging and negatively correlated with erectile function

The typical SWE images of the corpus cavernosum in each age group (left side, longitudinal view) were shown in **Figure 1a–1g**. With aging, the CCYM of the penis gradually increased, as shown by the change from blue to indigo on the SWE color scale. As shown in **Figure 1h**, the YM of the corpus cavernosum (mean ± s.d.) in boys aged 5–10 years was 9.06 ± 0.92 kPa (we did not evaluate the erectile function of boys in this age group because they did not have sex). Men aged 20–29 years had the best erectile function, with an IIEF-5 score (mean ± s.d.) of 22.23 ± 2.92. The CCYM (mean ± s.d.) in this age group was 11.88 ± 1.25 kPa, which was significantly higher than that of the 5–10 years old group. Erectile function declined in the 30–39 years old group, with an IIEF-5 score (mean ± s.d.) of 21.33 ± 3.46 and an CCYM (mean ± s.d.) of 14.37 ± 1.10 kPa. Similar changes with increasing age were observed in the 40–49 years, 50–59 years old, 60–69 years old, and ≥70 years old groups. Therefore, aging was positively correlated with YM ($r = 0.949$, $P < 0.01$; **Figure 1h**) but negatively correlated with erectile function ($r = -0.843$, $P < 0.01$; **Figure 1i**). However, we found that the CCYM was negatively correlated with erectile function ($r = -0.737$, $P < 0.01$; **Figure 1j**).

Table 1: Young's modulus of corpus cavernosum in healthy study participants in different age groups

Age (year)	*Transverse view (kPa), mean±s.d.*		*Longitudinal view (kPa), mean±s.d.*		*F*	*P*
	Left	*Right*	*Left*	*Right*		
5–10	9.06±0.92	9.02±1.37	9.01±1.51	9.09±1.98	0.084	0.968
20–29	11.88±1.25	12.02±1.07	11.19±1.70	12.19±1.52	0.091	0.965
30–39	14.37±1.10	14.27±1.53	14.30±1.71	14.40±1.62	0.282	0.838
40–49	17.10±1.64	16.35±1.43	17.35±1.56	17.15±1.28	0.098	0.938
50–59	21.48±2.03	21.61±2.06	21.69±2.64	21.70±2.52	0.595	0.619
60–69	25.00±2.15	24.88±1.79	25.08±2.02	24.39±1.98	0.271	0.851
≥70	28.12±1.62	27.83±1.42	28.29±1.71	27.96±1.42	0.398	0.728
H	125.31	121.89	126.25	125.55	NA	NA
P	<0.001	<0.001	<0.001	<0.001	NA	NA

s.d.: standard deviation; NA: not available

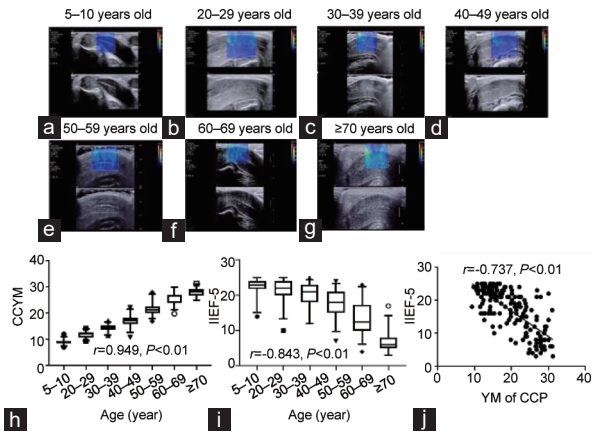

Figure 1: Typical SWE images of the CCP in each age group (left side, longitudinal view). With aging, the color of the CCP on the SWE color scale gradually changed from blue to indigo in (**a**) 5–10 years old, (**b**) 20–29 years old, (**c**) 30–39 years old, (**d**) 40–49 years old, (**e**) 50–59 years old, (**f**) 60–69 years old, and (**g**) ≥70 years old groups, respectively. (**h**) The YM was positively correlated with age ($r = 0.949$, $P < 0.01$). (**i**) Erectile function was negatively correlated with age ($r = –0.843$, $P < 0.01$). (**j**) The SWE measurement of the CCP was negatively correlated with erectile function ($r = –0.737$, $P < 0.01$). SWE: shear wave elastography; CCP: corpus cavernosum of the penis; YM: Young's modulus; IIEF-5: the International Index of Erectile Function-5.

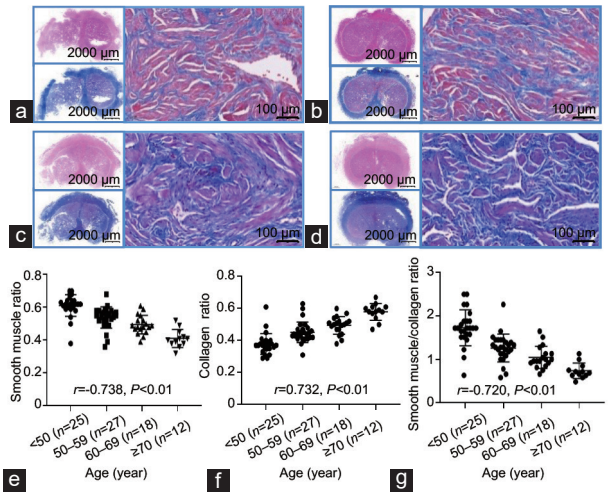

Figure 2: Wide view (scale bars = 2000 μm) of H&E and Masson's staining and magnified view (scale bars = 100 μm) of Masson's staining of the CC in different age groups. The CCs of (**a**) a 47-year-old, (**b**) a 55-year-old, (**c**) a 65-year-old, and (**d**) an 83-year-old patients, respectively. (**e**) The percentage of smooth muscle (red) content decreased with age ($r = –0.738$, $P < 0.01$). (**f**) The percentage of collagen (blue) content increased with age ($r = 0.732$, $P < 0.01$). (**g**) The smooth muscle/collagen ratio decreased with age ($r = –0.720$, $P < 0.01$). H&E: hematoxylin and eosin; CC: corpus cavernosum.

Histological changes in the CC in humans of different ages

It is known that the CCs undergo natural aging over time.[9,10] The CCYM had a positive correlation with aging, suggesting that an increase in YM might be a sign of CC aging. To further explore the underlying histological changes in the CC in subjects of different ages groups and with different YM measurements, we performed histological examinations of resected human penile specimens.

Eighty-two human penile CCs in different age groups were collected for H&E and Masson's staining. The CCs of younger subjects contained more smooth muscle (in red) and more spaces than those of older subjects (**Figure 2a**–**2d**). The percentage of smooth muscle (in red) content significantly decreased with age ($r = –0.738$, $P < 0.01$; **Figure 2e**), whereas the percentage of collagen (in blue) content significantly increased with age ($r = 0.732$, $P < 0.01$; **Figure 2f**). The smooth muscle/collagen ratio significantly decreased with age ($r = –0.720$, $P < 0.01$; **Figure 2g**).

Histological and YM measurements in rats of different ages

Since all the human CC pathology samples were from surgical resections of penile carcinoma without preoperative SWE examinations, we performed an animal study to further investigate the underlying histological causes that could be responsible for the CCYM changes observed during the aging process.

As shown in **Figure 3**, the CCYM (mean ± s.d.) increased with age ($r = 0.934$, $P < 0.01$), measuring with 11.98 ± 1.54, 17.27 ± 1.55, and 27.47 ± 1.97 in the penises of 3-, 12-, and 24-month-old rats, respectively. The percentage of smooth muscle content significantly decreased with age ($r = –0.423$, $P < 0.01$), and the percentage of collagen content significantly increased with age ($r = 0.557$, $P < 0.01$). The ICP/MAP ratio significantly decreased with age ($r = –0.808$, $P < 0.01$).

DISCUSSION

The aging of organs and tissues in the human body is a physiological process that results in a gradual decline in various functions.[20,21] This aging process applies to the penile CC and results in a decline in erectile function.[8–10] SWE is a noninvasive method to measure differences in tissue structure, and it is widely used in the differential diagnosis of breast,[22] prostate,[23] and liver[24] diseases. In the current study, we used SWE to evaluate the tissue structure of the CC.

Our research confirmed that the CCYM increased with age, and this change was accompanied by a decline in erectile function. It is known

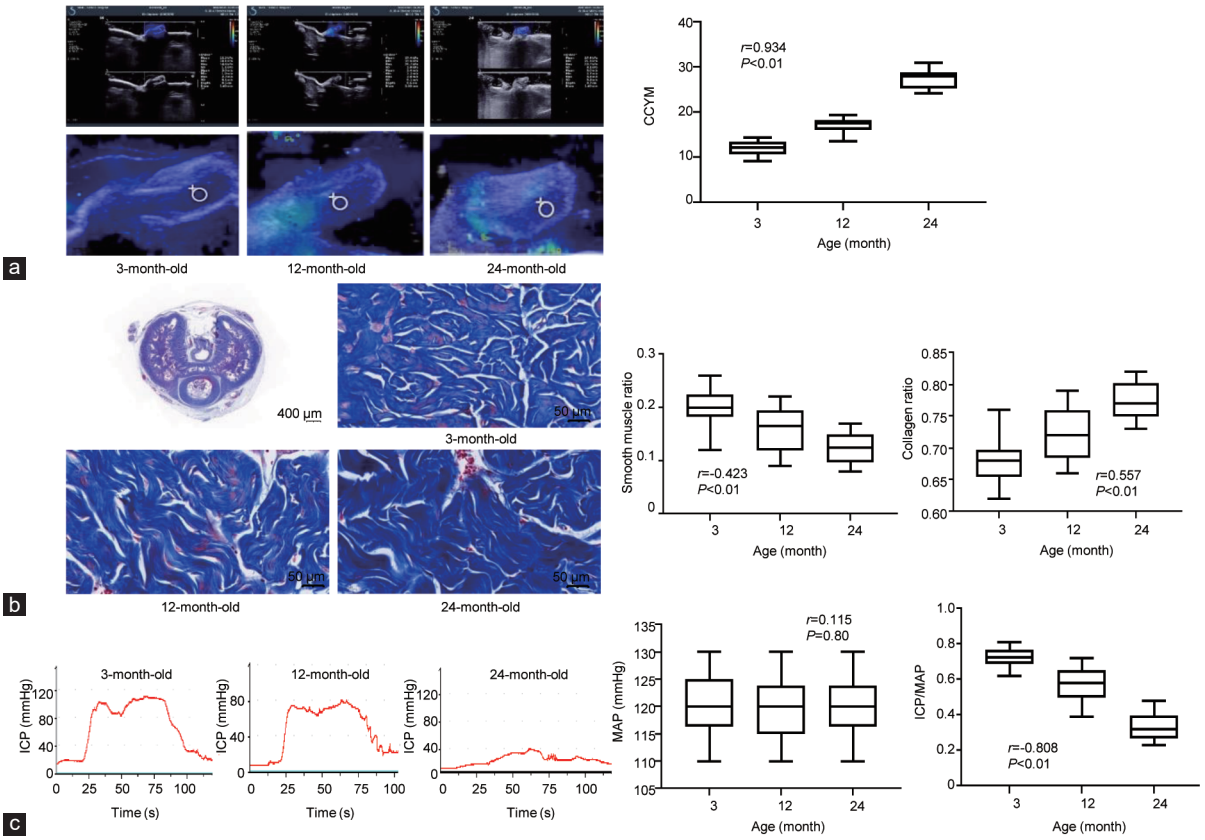

Figure 3: SWE and histological examinations of penile CCs and assessment of erectile function in experimental rats. (**a**) 2D ultrasonic and SWE imaging of the CCs of 3-, 12-, and 24-month-old rats (upper); magnified SWE imaging (lower). The YM of the CC increased with age ($r = 0.934$, $P < 0.01$). (**b**) Wide view (scale bar = 400 μm) and magnified view (scale bars = 50 μm) of Masson's staining of the CCs of 3-, 12-, and 24-month-old rats. The percentage of smooth muscle content decreased with age ($r = –0.423$, $P < 0.01$), and the percentage of collagen content increased with age ($r = 0.557$, $P < 0.01$). (**c**) Erectile function in 3-, 12-, and 24-month-old rats. With age, the MAP remained unchanged, while the ICP/MAP ratio decreased ($r = –0.808$, $P < 0.01$). SWE: shear wave elastography; CC: corpus cavernosum; YM: Young's modulus; CCYM: YM of the CC; ICP: intracavernous pressure; MAP: mean arterial pressure; 2D: two dimensional.

that the tissue components of the CC undergo physiological aging, which includes a decrease in smooth muscle mass, a reduction in the expression of elastic fibers, and an increase in collagen content,[8–10,25] and these structural changes lead to a decline in erectile function. Because the stiffness of collagen on SWE is higher than that of smooth muscle,[14,15] the increase in collagen content and decrease in smooth muscle content with age might explain the increased CCYM. We confirmed that the structural changes in the CC could be measured noninvasively and quantitatively by SWE, which provided an objective method to assess the progression of aging in the CC.

Several studies have reported that SWE can be used to measure the stiffness of the CC. Inci *et al.*[14] confirmed that age was positively correlated with the stiffness of the penis as measured by SWE. The stiffness of the CCs as measured by SWE significantly increased after the age of 50 years. In our study, the CCYM was measured in different age groups, and we found that its values increased steadily with age. Zhang *et al.*[25] reported a negative correlation between age and CC stiffness measured by SWE, which was different from our study results. This difference might be due to the small number of volunteers aged >50 years included.[25] In agreement with our results, Ferrer *et al.*[26] reported that the smooth muscle content of the penile CCs decreased during the process of aging, while the collagen content increased. Calabrò *et al.*[27] demonstrated that the erectile function of rats decreased significantly with age, and light microscopy showed signs of degenerative changes in elastic fibers with age. These structural changes were an important cause of the decline in erectile function. In general, these CC structural changes can be noninvasively and quantitatively detected by SWE.

This study demonstrated that SWE could quantitatively evaluate the degree of aging of the CC. The CCs from the surgical specimens revealed histological changes over the course of the aging process. However, there were no SWE data from the human surgical specimens. Therefore, we performed an animal study to investigate the relationships between YM and underlying histological changes in rats of different ages.

We found a decrease in smooth muscle content and an increase in collagen content during the aging process in rats. The CCYM was positively correlated with collagen content and negatively correlated with smooth muscle content. The YM of collagen is higher than that of smooth muscle.[14,15] Therefore, changes in smooth muscle and collagen content could be the histological basis of CC aging. An increase in the YM could also be a marker for aging of the CCs. This age-related change can be noninvasively and quantitatively detected by SWE, making SWE a desirable measurement method for research on the aging of the penile corpus cavernosum.

In both male volunteers and SD rats, erectile function was negatively correlated with CCYM and CC aging. It is well known that smooth muscle relaxation is the key process in penile erection.[28] A decrease in smooth muscle content will cause ED with an increased YM. Therefore,

the YM of the CC could be a theoretical marker of erectile function. The degree of aging of the CC as detected by SWE could reflect erectile function, which might provide a new method to noninvasively evaluate erectile function. However, further investigations on the relationship among erectile function, the YM of the CC, and histological changes in animal models of ED are needed to confirm the results of this study.

The limitations of our study include the single-center design and the small sample size. Ultrasound examination also introduced inter- and intra-observer variability. Furthermore, information on the participants' sexual activity, including sexual frequency and the duration of abstinence, was not recorded, which might affect the YM of the CC. We did not perform SWE measurements and histological examinations in the same patients, and the relationship between SWE and histological examinations was established from rats studied at a few different ages. Furthermore, we did not perform a laboratory test for sex hormones in the study participants; these hormones might affect erectile function and SWE measurements. Finally, SWE examination is very sensitive, and an experienced doctor is needed to perform it, which limits the clinical use of this technique.

CONCLUSIONS

SWE can noninvasively and quantitatively evaluate the aging of the CC. Increased collagen content and decreased smooth muscle content may be the histological basis for aging-related changes in the CC and the concurrent increase in its YM.

AUTHOR CONTRIBUTIONS

LY and LTR participated in the design of the trial, conducted the data acquisition, interpreted and analyzed the data, and drafted and revised the manuscript; HC, FW, and GXL designed the study and contributed to the study materials. LTR and KW pointed out deficiencies and ameliorated the manuscript. HC, GXL, and FW guided the experimental directions and drafted the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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