Original Article

Whole body vibration training promotes proprioceptive pathway for the treatment of stress urinary incontinence in rats

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Background: Stress urinary incontinence (SUI) is the most ubiquitous form of urinary incontinence in women. The therapeutic management of patients with SUI is challenging. The aim of this study is to evaluate the efficacy of whole body vibration training (WBVT) for SUI.

Methods: Thirty-five female rats were randomly divided into a sham group (Sham group, n=5), SUI + WBVT group (n=15) and SUI + whole body rest group (SUI + WBR group, n=15). The SUI + WBVT group was trained as follows: frequency 30 Hz, amplitude four mm, one min/repeat, four min rest, repeated 10 times, five days/week. After the intervention, five rats were taken on the 7th, 14th and 21st day to observe the urodynamic changes, levator ani muscle and dorsal root ganglia (DRG) morphology, and to observe the expression of neurotrophic factor-3/tyrosine protein kinase C (NT-3/TrkC) by Western blot.

Results: The urodynamic results showed that the difference in bladder leak point pressure/abdominal leak point pressure (BLPP/ALPP) between the Sham group and the SUI + WBR group was statistically significant (P<0.001) on 7th day, indicating successful modeling. The BLPP/ALPP of the SUI + WBVT group and the SUI + WBR group improved on 7th, 14th, and 21st day, and the BLPP/ALPP of SUI + WBVT group was higher than the SUI + WBR group. Compared with the Sham group, pathological changes appeared in the muscle shuttles in the SUI + WBVT group and SUI + WBR group. Western blot showed a gradual up-regulation of NT-3/TrkC.

Conclusions: WBVT can be used to treat SUI by affecting the expression of NT-3/TrkC, improving the structural morphology of the proprioceptors, and restoring the urinary control function. This study provides evidence for the clinical practice of WBVT. Future studies could further refine the behavioral and electrophysiological aspects of the assessment.

Keywords: Stress urinary incontinence (SUI); whole body vibration training (WBVT); proprioception; neurotrophic factor-3 (NT-3)

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Introduction

Worldwide, urinary incontinence is a common disease that affects millions of people, and it is more common in women (1,2). Stress urinary incontinence (SUI) is the most common, with the complaint of involuntary leakage of urine during coughing, sneezing, and other times when the abdominal pressure is increased, and accounting for 63% of all types of urinary incontinence (3). SUI is not fatal, but it can have a significant negative impact on women's physical and mental health, and reduce their quality of life. In addition, SUI carries a heavy financial burden, with an annual healthcare burden of $12 billion in the United States alone (4). In addition, the healthcare costs associated with SUI are expected to increase in the coming decades with the aging of society and the desire for a higher quality of life (5).

Vaginal delivery is an independent risk factor for the development of SUI (6). During vaginal delivery, the pelvic floor muscles, fascia and nerves are overstretched, resulting in loosening of the vaginal walls, rupture of the pelvic floor fascia, tearing of the levator ani muscle and enlargement of the levator ani muscle fissure (7). Multiple damages to the pelvic floor structures ultimately result in SUI due to dysfunction of the urethral sphincter closure system, weakening of the urethral support system and delayed nerve conduction or denervation (8). The pathophysiological mechanisms leading to the development of SUI include anatomical, functional (9) and neurophysiological (damage to the lower urinary tract urinary control nerve circuit and defects in proprioceptive pathways) (10). An in-depth understanding of these mechanisms contributes to a comprehensive understanding of the pathogenesis of SUI.

Proprioception, the sensory ability to perceive position and movement (11). Proprioceptive organs are mainly located in muscles and joints, where most of the proprioceptive feedback comes from the mechanoreceptors in skeletal muscles—muscle spindles and Golgi tendon organs (12). Neurotrophic factor-3 (NT-3) is a member of the neurotrophic factor family that plays a crucial role in promoting and regulating the survival of sensory neurons and target tissues, such as skeletal muscle (13). NT-3 and its specific receptor, tyrosine protein kinase C (TrkC), play an important role in neurotransmission in proprioception, proprioceptive rehabilitation, and nerve regeneration (14). Studies have shown that pathological alterations in the morphology of the muscle spindles and Golgi tendon organs and reduced NT-3 expression were found in a SUI model of rat simulating birth injury (15). This results in symptoms of urine leakage in women who are unable to control pelvic floor contractions in a timely manner when abdominal pressure increases (10).

Therefore, how to strengthen the pelvic floor muscles and improve the control of the pelvic floor muscles to grasp the correct timing of contraction is very important for the treatment of SUI. Currently, pelvic floor rehabilitation methods available in the clinic include: behavioural therapy, Kegel exercises, and biofeedback electrical stimulation, but clinical efficacy varies (4). Whole body vibration training (WBVT) is a novel neuromuscular training technique in which patients stand on a vibration platform and mechanical vibration waves cause excitation of the muscle spindle, leading to an increase in motor unit recruitment and synergistic contraction of the muscles (16,17). These physiological changes could lead to more effective proprioceptive feedback and due to the activation of motor neurons, WBVT is believed to enhance skeletal muscle strength, improve motor control, and improve postural balance (18,19). Based on this, a few scholars have utilized WBVT to treat SUI in the clinic and achieved significant efficacy (20,21). Currently, it is not clear how WBVT treats SUI at the level of molecular mechanisms, which should be further explored in depth to provide a supportive basis for the broader clinical application of WBVT.

The aim of this study was to investigate whether WBVT can improve the symptoms of SUI by up-regulating NT-3/TrkC, improving the structure, morphological restoration,

Highlight box

Key findings

- The mechanism that enables whole body vibration training (WBVT) to improve stress urinary incontinence (SUI) is achieved by improving the morphology of the proprioceptors in the levator ani muscles, the proprioceptive pathways and their signaling molecules.

What is known and what is new?

- Current literature describes an improved urine leakage symptoms and quality of life among women with WBVT for SUI.
- This study demonstrated that WBVT improves urodynamics in SUI, possibly due to improving proprioceptive pathways and associated molecules.

What is the implication, and what should change now?

- WBVT is a non-invasive rehabilitation method that may help on the recovery of SUI.
- Further expanded clinical trials are needed to confirm the efficacy of WBVT in SUI.

and urinary control function of the proprioceptors. We present this article in accordance with the ARRIVE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-675/rc).

Methods

Experimental model

All procedures were approved by the Experimental Animal Ethics Committee of Central South University and conducted in compliance with Chinese or institutional guidelines for the care and use of animals (Animal Ethics Review No. CSU-2022-0603). Thirty-five female Sprague Dawley rats (nine weeks old, non-pregnant and weight between 200–250 grams) were randomly divided into sham group (n=5), SUI + WBVT group (n=15) and SUI + whole body rest (WBR) group (n=15). The SUI group received a vaginal delivery with the method of simulating the birth injury by the secondary vaginal balloon dilatation. All rats were housed at three rats per cage, with free access to tap water and food at 20–26 ℃, 40–60% relative humidity and a 12-hour light/dark cycle. All rats were purchased at a weight of 150–180 grams and were acclimatized to 200–250 grams after one week of feeding. The method used to establish SUI model rats was based on a previous report (22). It simulates the damage to the pelvic floor caused by vaginal birth; however, the anatomy of the pelvic floor is different from that of humans and can only simulate the disease state to the greatest extent possible (23). A protocol was prepared before the study without registration.

Training programs

The whole body vibration instrument was provided by Zhengzhou Yufeng Medical Technology Co., Ltd. (Model: Y-V301). The SUI + WBVT group was trained for 7, 14, and 21 days, respectively. A homemade box was glued to the vibration platform at the corresponding amplitude (four mm) line. The rats were placed into the box to keep them in the upright position. The WBVT training program was as follows: frequency of 30 Hz, amplitude of four mm, one min/trip, four min of rest between the groups, a group of ten trainings, and a group of one training per day, five days/week.

The SUI + WBR group simply placed the rats in the box and kept them in the upright position for 50 min without vibration training.

Urodynamic testing and analysis

An Alcott-Cystometrography (ALC-CMG) Small Animal Intravesical Pressure Measuring Instrument (Shanghai Alcott Biotechnology Co., Ltd., Shanghai, China) was used for urodynamic analysis. Urodynamic measurements were performed in the Sham group at 7^{th} day, and in the WBVT/WBR group, five rats were randomly selected from each group at 7^{th} ,14^{th} and 21^{st} day. Rats were injected intraperitoneally with 10% urethane (1.2 g/kg) and placed in the supine position after complete anesthesia. The urethral opening was sterilized with iodophor, and an F3 ureteral catheter coated with liquid paraffin was inserted into the urethra at a depth of about two-three cm. The catheter was held in place by adhesive tape; if urine flowed out of the catheter, this indicated that the catheter was in the bladder. After the bladder was emptied of residual urine by gentle pressure, the end of the F3 ureteral catheter was connected to the ALC-CMG device through a tee tube, and the other port of the tee tube was connected to a microinfusion pump. Saline was infused into the bladder at a rate of 0.2 mL/min. The amount of saline injected was recorded when the first drop of urine was seen at the urethral orifice, which was considered to be the maximum bladder volume (MBV), and the intravesical pressure at that time point was recorded as the bladder leak point pressure (BLPP). Thereafter, we emptied the bladder and infused saline up to half of the MBV volume and manually pressed slowly on the epigastric region of the rats to slowly increase the abdominal pressure to simulate the Valsalva maneuver. When urine was overflowed, the bladder pressure at that time point was regarded as the abdominal leak point pressure (ALPP).

Tissue processing

After measuring the urodynamics, the rats were euthanized. The lower abdomen of rats was prepared and sterilized, and then incised vertically with scissors to the external urethral opening. The pubic symphysis was localized and dissected, and the urethra, vagina, and rectum were sequentially freed to expose the levator ani muscles (two on each side)—pubococcygeus and iliococcygeus. Located the muscle bellies, and then the ends of the muscles on both sides were quickly clamped and separated with scissors and toothless forceps. One side was quickly put into liquid nitrogen and transferred to –80 ℃ refrigerator. The other side was quickly placed in four percent paraformaldehyde overnight.

The rats were quickly turned over and placed in the prone position, and according to the spinal mobility and anatomical localization, the L6 and S1 vertebrae were positioned. Peeling off the muscles, the plate, spinous process and transverse process, then the bulging portion of the nerve, which was the L6-S1 dorsal root ganglia (DRG), were ultimately exposed. The L6-S1 DRG was placed into the 4% paraformaldehyde quickly overnight.

Hematoxylin and eosin staining

One side of the levator ani muscle was stained using hematoxylin and eosin (H&E) staining. The slide was fixed and photographed under light microscopy. At least five fields of view from each muscle preparation were captured and analyzed.

Immunohistochemistry for parvalbumin (PV) staining

To examine changes for proprioceptive neuron, DRG was taken for immunohistochemical staining with a rabbit anti-rat PV (provided by Wuhan Proteintech Co., Ltd., Wuhan, China). Five representative regions were randomly selected for description and analysis from consecutive horizontal frozen sections of DRG tissue.

Western blot

Levator ani muscle tissue was homogenized in radioimmunoprecipitation cell lysis buffer containing phosphatase and protease inhibitors. Bicinchoninic acid (BCA) method was performed to determine protein concentration of each sample. A total of 50 μg of protein lysate for each sample was loaded and run on a sodium dodecyl sulfate-polyacrylamide gel. After the gel was finished running, protein was transferred to a polyvinylidene difluoride membrane. After membrane washing, rabbit anti-rat TrkC (provided by Wuhan Proteintech Co., Ltd., AF300917, 1:100) and rabbit anti-rat NT-3 (provided by Wuhan Proteintech Co., Ltd., YT5911, 1:100) were added and incubated overnight at four degrees centigrade. Then, membranes were washed again and incubated with horseradish peroxidase (HRP)-goat anti-rabbit secondary antibody at room temperature. The blots were visualized by using an electrophoresis gel imaging analyzer. Values were expressed as the relative expression level for each protein between the optical density of the target protein and that for glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

Statistical analysis

SPSS 26.0 was used for statistical analysis of data in all groups. Values were reported as mean ± standard deviation (SD), and comparisons between groups were carried out with Student's *t*-test or one-way ANOVA when appropriate. Statistical differences were considered as significant at P values <0.05.

Results

Urodynamic analysis

On 7th day after intervention, BLPP and ALPP were significantly lower in the SUI + WBR/WBVT group compared to the Sham group, the difference was statistically significant (P<0.001).

After 7 days of WBVT treatment, BLPP/ALPP improved significantly compared with the SUI + WBR group, and the difference was statistically significant (P=0.002/0.004). After 14 days of WBVT treatment, BLPP/ALPP improved significantly compared with the SUI + WBR group, and the difference was statistically significant (P=0.02/0.04). After 7 and 14 days of WBR intervention, BLPP and ALPP gradually improved, which indicated the self-healing ability of this SUI model. After 21 days of intervention, BLPP showed an increasing trend but was not statistically significant (P=0.13), and the difference in ALPP was statistically significant (P=0.02) (*Table 1*).

HE staining

Figure 1 demonstrates the morphologic structure of the levator ani muscle cross section in each group. The results showed that there was a shuttle capsule structure with regular morphology in the middle of the muscle fibers of the levator ani muscle in the Sham group in *Figure 1A*. It was the normal structure of the levator ani muscle shuttle. The muscle fibers in the shuttle could be divided into nuclear pocket fibers and nuclear chain fibers, both of which were wrapped by the outermost layer of the shuttle capsule, and the morphology of the shuttle capsule was regular. However, the muscle shuttle in SUI + WBR/WBVT showed different degrees of morphological variations, which were mainly manifested as the thinning of the shuttle capsule, irregular polygonal structure, and inward concavity (*Figure 1B-1D*), and the gap between the muscle fibers in the shuttle increased or clustered (*Figure 1B-1F*), which suggested that the

Table 1 Comparison of urodynamic indices among Sham, SUI + WBR and SUI + WBVT groups

Date	Parameter	Sham group	SUI + WBR group	SUI + WBVT group	t	P
7 d	BLPP	45.307±1.220	25.462±1.288*	29.991±1.900*	−4.411	0.002
	ALPP	52.226±1.609	39.627±1.023*	41.959±0.770*	−4.071	0.004
14 d	BLPP	–	28.657±1.091	31.265±1.636	−2.966	0.02
	ALPP	–	39.523±1.909	42.093±1.357	−2.454	0.04
21 d	BLPP	–	36.649±4.245	40.832±3.551	−1.69	0.13
	ALPP	–	50.035±0.887	52.030±1.330	0.681	0.02

Data are shown as mean ± standard deviation. Values are expressed in mmH2O and analyzed with a student *t*-test; *, compared with Sham group, the BLPP/ALPP of SUI + WBR/WBVT group were significantly difference and P value are all <0.001. SUI, stress urinary incontinence; WBR, whole body rest; WBVT, whole body vibration training; BLPP, bladder leak point pressure; ALPP, abdominal leak point pressure.

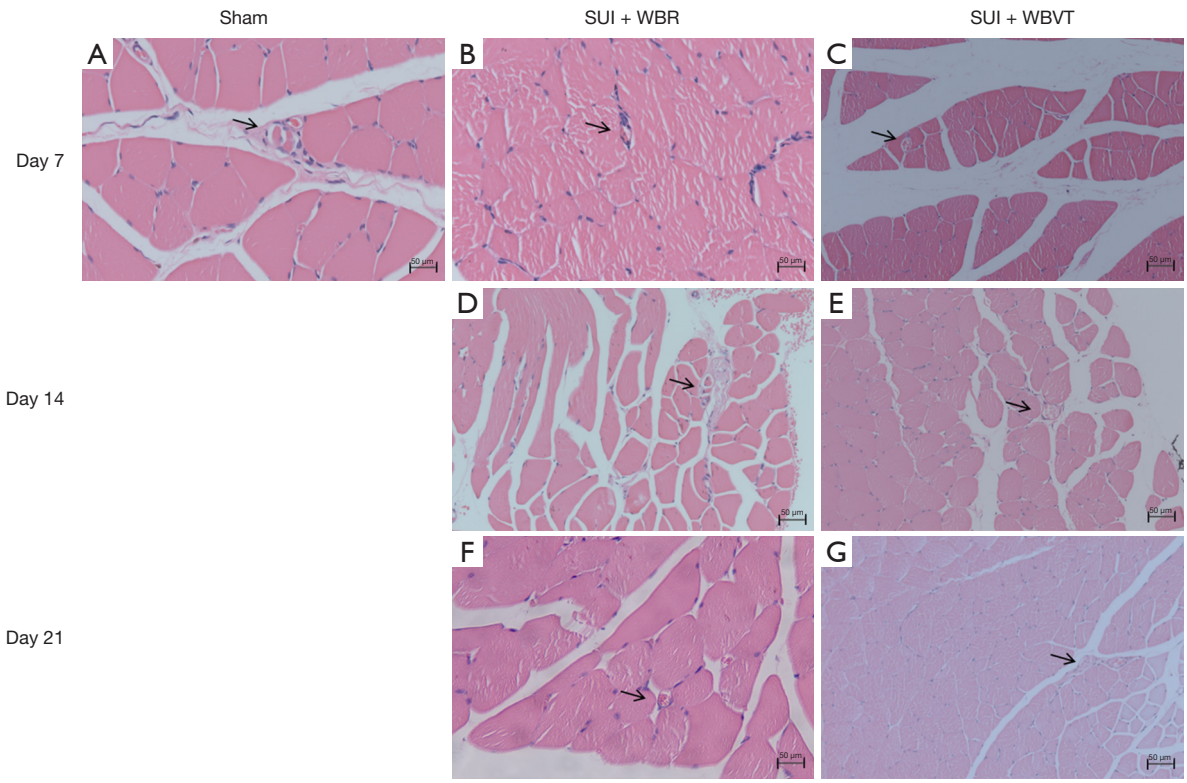

Figure 1 Morphological changes of muscle shuttles in the levator ani muscles in each group; the positions indicated by arrows are muscle shuttles, scale bar =50 μm. Each levator ani muscle was stained by hematoxylin-eosin and fixed on a slide, observed by light microscope and labeled with the position of the muscle shuttles. SUI, stress urinary incontinence; WBR, whole body rest; WBVT, whole body vibration training.

morphology and structure of the anus-recti muscle shuttle could be damaged by the SUI modeling, which might affect its ontogeny. This result suggested that after SUI modeling, the morphology and structure of the levator ani muscle shuttle could be damaged, which might affect its proprioceptive conduction function. Whereas the *Figure 1G* shows a more complete structure of the muscle shuttle and a uniform gap between the muscle fibers

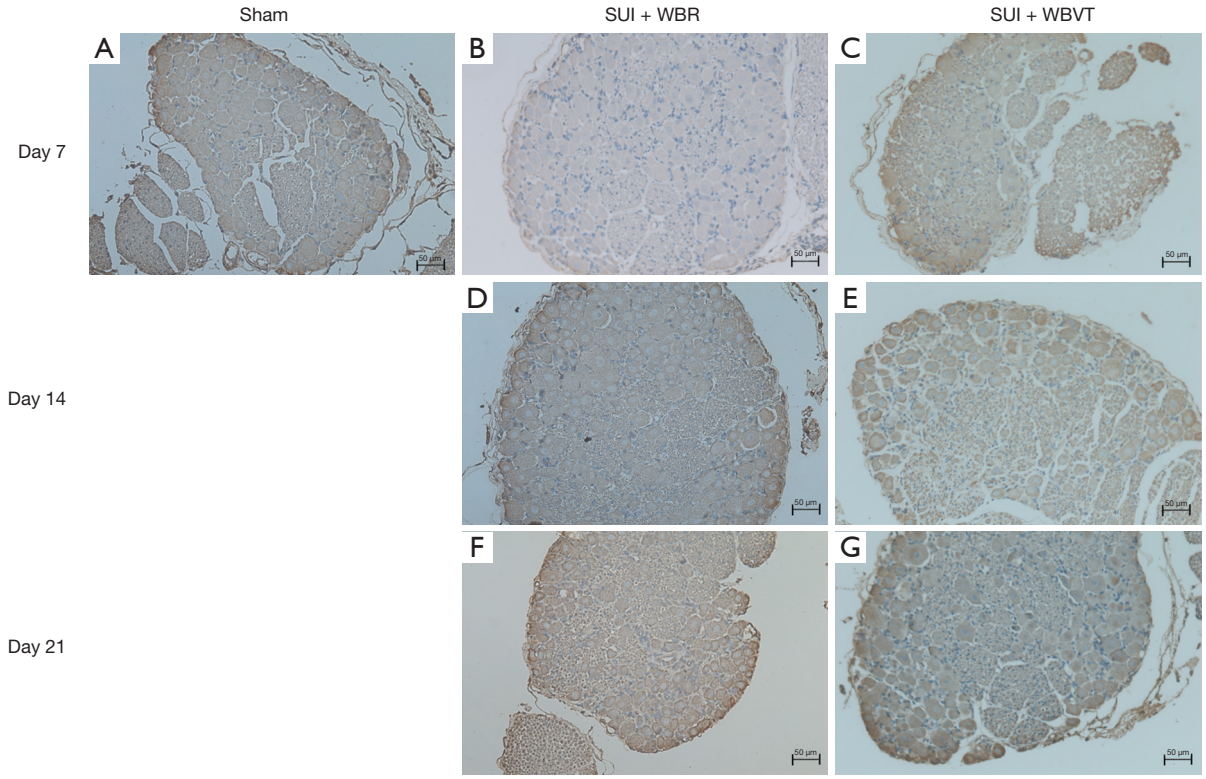

Figure 2 Expression results of PV proteins in L6-S1 DRG tissues of rats in each group, scale bar =50 μm. DRG samples were subjected to immunohistochemical staining using a rabbit anti-rat PV antibody. The stained samples were then observed under a fluorescence microscope. SUI, stress urinary incontinence; WBR, whole body rest; WBVT, whole body vibration training; PV, parvalbumin; DRG, dorsal root ganglia.

within the shuttle, which indicated that WBVT might be able to improve the morphology of the muscle shuttle and achieved the purpose of treating SUI.

Immunohistochemical staining

Figure 2 shows the PV protein expression level in L6-S1 DRG of rats in each group. The positive signal of PV protein was the strongest in the Sham group (*Figure 2A*). After 7 days, the PV protein expression level of SUI + WBR/WBVT was significantly decreased, with the most obvious decrease in the SUI + WBR group. The above also demonstrated that SUI modeling led to a certain degree of reduction in the proprioceptive transduction function of the levator ani muscle. However, the positive signal of PV protein was gradually enhanced over time and recovered faster after treatment with WBVT (*Figure 2E,2G*), which also proved that WBVT could have a positive effect on the proprioceptive pathway.

Western blot

The expression of NT-3 and TrkC in the levator ani muscles of rats in each group was determined at the protein level, and the results are shown in *Figure 3*. After 7 days, the protein expression of NT-3 and TrkC in the levator ani muscle shuttles in the SUI + WBR/WBVT group was decreased relative to the Sham group ($P<0.05$). After 14 and 21 days of intervention, NT-3 and TrkC protein expression of rat levator ani muscle shuttles in the SUI + WBVT group was upregulated relative to that of rats in the SUI + WBR group ($P>0.05$); and NT-3 and TrkC protein expression of rat levator ani muscle shuttles in the SUI + WBVT group was upregulated relative to that of rats in the Sham group ($P<0.05$).

Discussion

Since mechanical load and stretching of the pelvic floor as

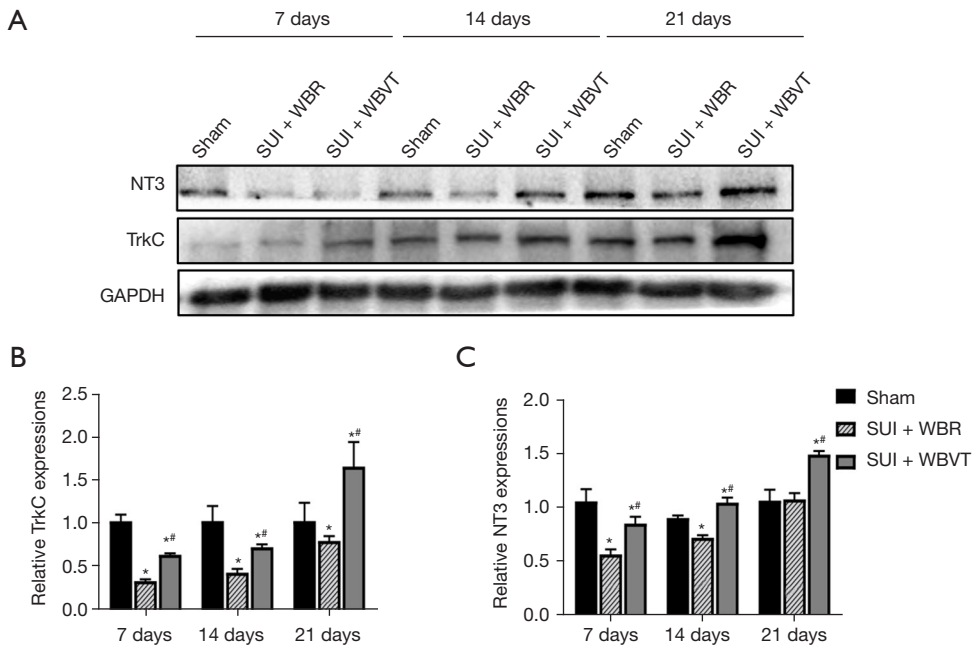

Figure 3 Expression of NT-3 and TrkC proteins in the muscle shuttles of the levator ani muscles of rats in each group. *, P<0.05 compared with Sham group; #, P<0.05 compared with SUI + WBVT group. X axis represents days of intervention. SUI, stress urinary incontinence; WBR, whole body rest; WBVT, whole body vibration training; NT-3, neurotrophic factor-3; TrkC, tyrosine protein kinase C.

caused by vaginal delivery are known to increase the risk of SUI (24), in this study, we constructed SUI model rats by secondary vaginal balloon dilatation to simulate birth injury method. On day 7 after completion of modeling, BLPP and ALPP were significantly reduced in both the SUI + WBVT group and the SUI + WBR group compared with the Sham group (P<0.001), indicating the success of the SUI model. Normal urinary control depends on the proper functioning of two systems: the sphincter system and the support system. The sphincter system prevents leakage by contracting the urethra so that the urethral closure pressure is greater than the intravesical pressure; the support system consists of the anterior vaginal wall, connective tissue and pelvic floor muscle (25). Normal nerve conduction was also important in activating the supporting structures during increased abdominal pressure (25). If there is an injury to one or more of these components, symptoms of urinary incontinence can occur.

In addition to abnormalities in pelvic floor structures, the activation and coordination of the patients' pelvic floor muscles are impaired in patients with SUI compared to normal women, i.e., sensory-motor control of the pelvic floor muscles is diminished in patients with SUI (26). Good motor control relies on continuous signaling between motor and sensory systems, and motor control adaptations are inevitably associated with somatosensory processing adaptations, with proprioception being the key sensory feedback system (27). Patients with diminished or absent proprioception experience motor control deficits, such as deficits in plyometric control, coordinated movement, and positional awareness (28). Proprioception is provided by deep and superficial mechanoreceptors, and the muscle shuttle, located in the muscle belly of the skeletal muscle, acts as the primary proprioceptor (27). When the muscle shuttle transmits the collected information via the DRG to the dorsal horn of the spinal cord and up to the higher centers of the brain (brainstem, cerebral cortex), the afferent proprioceptive sensations (positional sensation, kinesthetic sensation) are centrally integrated to form efferent signals to innervate the corresponding muscles (29,30). Correct signaling requires an intact neuroreflex pathway. Our results showed that in the first week, the morphology of the proprioceptors (muscle spindles) in the levator ani muscles of the SUI + WBVT/WBR group showed pathologic changes compared to the Sham group: irregular morphology, volume reduction, and aggregation of internal structures. That is, at the initial stage, the receptors were abnormal, which led to the symptoms of urine leakage in

patients with SUI who could not receive peripheral signals in a timely and systematic manner.

It has been shown that NT-3, a key induction signal for proprioceptive transduction, is produced by the intracellular muscle of the muscle shuttle in skeletal muscle (31), and when NT-3 expression is normal, proprioceptive nerve fibers can control target organs and play their physiological roles (32). In contrast, when NT-3 and its receptor TrkC expression is down-regulated, proprioceptive neurons in the DRG may undergo apoptosis, resulting in skeletal muscle proprioceptive defects (14). Conversely, when NT-3 and its receptor TrkC expression is up-regulated, it can promote neuronal development and maturation, maintain neuronal survival or improve proprioceptive function (14,32). The calcium-binding protein PV is a specific marker for proprioceptive neuronal cells in DRG (29). Our results showed that in the first week, the levator ani muscle shuttles in the SUI + WBVT/WBR group produced less NT-3 compared with the Sham group, and there was a corresponding decrease in the number of proprioceptive neurons labeled by PV proteins in the DRG, suggesting that the reduction of NT-3 in the SUI model rats affects proprioceptive neuron survival and negatively affects the functioning of the proprioceptive pathway.

WBVT is a proprioceptive stimulus with long-lasting postural effects, and the therapeutic effects exerted by WBVT may be a result of its influence on the neuromuscular system, proprioceptor improvement, and sustained stimulation of proprioceptive pathways are related (33). AS a new rehabilitation program, WBVT is becoming a key method in the rehabilitation of clinical patients (34). Through meta-analysis, Liu *et al.* found that during WBVT application, the active and synergistic muscles produce muscle contractions that cause changes in the length of the muscle spindle, activate the tendon apparatus, and cause the antagonist muscles to relax in a timely manner, which improves the efficiency of the muscle contractions and the co-ordination of the muscle activities, making them more precise. Therefore, it has significant effect in improving muscle strength and balance of the elderly (35). Zeng *et al.* also found by meta-analysis that WBVT activates a diversity of human skin and deep tissue receptors, increases sensory input to the central nervous system, promotes neuroplasticity, and improves stroke patients' proprioceptive and motor performance (33). However, some scholars have found that WBVT does not improve muscle strength and motor control in patients (36,37). As the underlying mechanisms of WBVT remains unclear, further exploration is necessary to better serve the clinic.

In this study, the results showed that after the SUI model rats were treated with WBVT, the urodynamic results of the rats gradually improved, the morphology of the levator ani muscle spindle gradually improved, the expression of NT-3 was gradually upregulated, and the corresponding proprioceptive neurons in the DRG were gradually improved, which indicated that WBVT may be able to achieve the therapeutic effect of SUI by affecting the expression of NT-3. Based on this, future research could focus on clinical trials of WBVT for SUI. Comparison with existing pelvic floor rehabilitation methods (Kegel exercises, pelvic floor biofeedback, etc.) to map out an individualized treatment plan for WBVT.

In summary, the results of our study provide evidence that WBVT can treat SUI by improving the proprioceptors and their signaling molecules. However, there are some limitations of this study. The rats used in this study are quadrupedal, and their pelvic floor anatomy and the pressures to which they are subjected are very different from those of humans (23). Therefore, subsequent studies need to explore animal models that are better matched to the clinical situation. In addition, the behavioral and electrophysiological aspects of rats were less studied in this study and further research could refine this aspect of the examination.

Conclusions

This study suggested that WBVT could promote the expression of NT-3/TrkC, improve the morphology of muscle spindles, enhance the conduction of proprioceptive pathway, and have positive therapeutic effects on the improvement of SUI. In future studies, the efficacy of WBVT can be validated in multi-center clinical trials compared to existing means of pelvic floor rehabilitation.

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Footnote

Reporting Checklist: The authors have completed the ARRIVE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-675/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-675/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-675/coif). The authors have no conflicts of interest to declare

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Experiments were performed under a project license (No. CSU-2022-0603) granted by the Experimental Animal Ethics Committee of Central South University, in compliance with Chinese or institutional guidelines for the care and use of animals.

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