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RESEARCH ARTICLE

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Botulinum neurotoxin type A improves vasti muscle balance, patellar tracking, and pain in patients with chronic patellofemoral pain

Saikat Pal[1] | Jang-Hwan Choi[2] | Scott L. Delp[3,4] | Michael Fredericson[4]

[1]Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, New Jersey, USA

[2]Division of Mechanical and Biomedical Engineering, Graduate Program in System Health Science and Engineering, Ewha Womans University, Seoul, South Korea

[3]Department of Bioengineering, Stanford University, Stanford, California, USA

[4]Department of Orthopaedic Surgery, Stanford University, Stanford, California, USA

Correspondence

Saikat Pal, Department of Biomedical Engineering, New Jersey Institute of Technology, 111 Lock St, Room 106, Newark, NJ 07102, USA.
Email: pal@njit.edu

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Abstract

The purpose of this study was to determine the effects of botulinum neurotoxin type A (BoNT-A) on vastus lateralis:vastus medialis (VL:VM) muscle balance, patellar tracking, and pain in patients with chronic patellofemoral (PF) pain. We recruited 13 participants (9 females, 4 males) with recalcitrant PF pain who underwent ultrasound-guided BoNT-A injections into the distal third of the VL muscle, followed by a 6-week home exercise program to strengthen their VM muscle. We imaged the participants in a C-arm computed tomography (CT) scanner before and after the intervention. We calculated VL:VM ratios from CT images from a supine, nonweight-bearing condition. We obtained patellar tilt and bisect offset values from CT images from an upright, weight-bearing condition. We recorded functional pain scores before, immediately after, and 2–4 years after the intervention. We classified the participants into normal tracking and maltracking groups based on their patellar tilt and bisect offset values. BoNT-A with home exercise reduced VL:VM ratio (18%; $p < 0.001$), patellar tilt (19%; $p = 0.020$), and bisect offset (5%; $p = 0.025$). Four participants classified as maltrackers before the intervention transitioned to normal tracking after the intervention. Functional pain scores improved immediately after the intervention (13%, $p < 0.001$) and remained improved at 2-year follow-up (12%, $p = 0.011$). Statement of Clinical Significance: This study provides new evidence in support of BoNT-A for treatment of PF pain. Classification of patients under weight-bearing conditions may identify individuals who will most benefit from a BoNT-A treatment.

KEYWORDS

anterior knee pain, botox, computed tomography, patellar maltracking, quadriceps

Saikat Pal and Jang-Hwan Choi are co-first authors.

1 | INTRODUCTION

Patellofemoral (PF) pain is a common overuse injury of the lower extremity.[1] It accounts for approximately one in four knee injuries diagnosed in sports medicine clinics,[2,3] with even higher rates reported in females.[4] PF pain is also the most common cause of medical discharge from military training.[5] This condition is characterized by retropatellar or peripatellar pain during activities such as walking, running, jumping, stair ascent and descent, and prolonged sitting and kneeling. The onset of PF pain leads to reduced participation in physical activity,[6] decreased quality of life,[7] and reduced career prospects.[5,6] In many patients, PF pain is a chronic problem with persistent clinical symptoms; up to 91% of patients report pain 4–20 years following initial diagnosis.[6–9] The persistence of symptoms in such a high percentage of patients highlights the challenges in determining the underlying cause of PF pain in individual patients and prescribing of effective treatments. This is especially challenging because the origins of PF pain remain unclear and likely differ between individuals.

Although there are several possible causes of PF pain, one mechanism that has received substantial attention from clinicians and researchers is elevated stress at the cartilage–bone interface due to excessive lateral tracking of the patella arising from an imbalance in the vasti muscles.[10–13] The vasti muscles contribute to extension of the knee and PF stability.[14] In particular, the vastus medialis oblique (VMO), the distal portion of the vastus medialis (VM) muscle, plays an important role in stabilizing the patella medially.[15] The VMO muscle is theorized to undergo rapid atrophy in response to injury, effusion, or persistent pain,[16] resulting in an imbalance in the vasti muscles, namely an increased ratio of the size of the vastus lateralis (VL) to the VM. This increased VL:VM ratio may contribute to excessive lateral displacement of the patella, resulting in reduced PF contact area, elevated cartilage stress, and pain.[17–19]

Clinical management of PF pain is often intended to alleviate PF joint stress by addressing lateral patellar maltracking.[20] A patient diagnosed with PF pain is usually first prescribed some combination of taping,[21,22] orthotic devices,[23,24] and physical therapy targeting hip and quadriceps strengthening or electromyography biofeedback.[25–27] However, conservative treatment options are ineffective in some patients.[28] A surgical intervention is a treatment option for patients who fail conservative measures.[20,28,29] Surgical methods to reduce lateral patellar maltracking are not always effective and expose patients to potential complications.[30,31] As such, it would be valuable to develop minimally invasive alternatives to surgical interventions for treatment of PF pain.

A promising minimally invasive treatment for PF pain is injection of botulinum neurotoxin type A (BoNT-A) into the distal third of the VL muscle.[32–36] BoNT-A is theorized to weaken the VL muscle, resulting in reduction in VL:VM ratio, lateral patellar tracking, and pain. Singer and colleagues[32–35] demonstrated that BoNT-A injections can reduce PF pain in patients who failed conservative treatment. This group reported reduced pain and improved joint function with no decrease in knee extension strength 24 weeks following a BoNT-A injection.[34] These improvements were sustained during long-term follow-up, with an average benefit of 34 months after injection in 44 out of 57 patients.[34] Singer et al.[32] also demonstrated significantly greater improvements in pain scores in patients injected with BoNT-A compared to patients injected with a placebo. These studies support the use of BoNT-A injection to treat PF pain; however, there is little evidence that BoNT-A alters an underlying mechanism of pain, namely reducing VL:VM ratio and lateral patellar tracking to alleviate PF pain. Accordingly, the aim of this study was to quantify the effects of BoNT-A on VL:VM ratio, patellar tracking, and pain in patients with chronic PF pain. We hypothesized that BoNT-A in combination with a 6-week home exercise program: (1) reduces VL:VM ratio; (2) reduces lateral patellar tracking (patellar tilt and bisect offset); and (3) improves functional pain score.

2 | METHODS

2.1 | Participant recruitment

We recruited 13 participants with chronic PF pain from the university's orthopedic clinics and sports medicine centers (Table 1). The participants included nine females (33.0 ± 9.6 years, 59.3 ± 5.4 kg) and four males (30.3 ± 12.7 years, 76.7 ± 6.5 kg). All participants were diagnosed by a sports medicine physician (M. F.) with 30 years of clinical experience. A participant was considered for this study if they were between 18 and 50 years of age, reported consistent PF pain for at least 6 months, and had failed to respond to conservative treatment, including at least 6 weeks of supervised physical therapy focused on hip and quadriceps muscle strengthening exercises. At the time of screening, a participant needed to experience reproducible anterior knee pain and record >3 on a 10-point visual analog scale in at least three of the following activities: (1) during or after physical activity, (2) during or after prolonged sitting, (3) walking up and down stairs, and (4) squatting. A participant was excluded if they had degenerative joint changes, other knee injuries, or prior treatment with BoNT-A. All participants were informed of all aspects of the study and provided prior consent according to the policies of our Institutional Review Board.

2.2 | BoNT-A intervention

All participants underwent ultrasound-guided BoNT-A injections to the distal third of the VL muscle. The study physician (M. F.) used

TABLE 1 Population characteristics of the patellofemoral pain participants (n = 13)

	Mean	SD	Range
Age (years)	32.3	9.9	20.0–45.0
Weight (kg)	65.8	10.5	54.5–83.9
Anterior Knee Pain Score	72.0	9.6	58.0–93.0

Abbreviation: SD, standard deviation.

500 u of BoNT-A (Dysport®; Ipsen Biopharmaceuticals) per participant, divided and injected across eight sites in the distal third of the VL muscle. This dosing is consistent with studies by Singer and colleagues.[32–35] The injections were guided using real-time ultrasound (Sonosite) to localize the VL muscle, and electromyography (Motion Lab Systems) was used to identify the motor points in the VL muscle. The study physician is board certified in sports medicine and electromyography.

2.3 | Home exercise program for VM strengthening

All participants were prescribed a 6-week home exercise program to strengthen their VM muscles.[34] A standardized exercise sheet with diagrams and written instructions was provided to each participant, and they were requested to record their home exercise routine using a logbook. Participants were encouraged to contact the study physician if they had questions regarding the exercise program. Before the beginning of the home exercise program, participants were provided with an explanation of the role of the quadriceps muscles in maintaining PF joint stability to maximize study compliance.

2.4 | C-arm computed tomography (CT) scanning

We imaged the quadriceps muscles and knee joints of all participants using a C-arm cone-beam CT scanner (Siemens Artis Zeeogo, Siemens Medical Solutions) at baseline (before BoNT-A injections) and after BoNT-A injections and 6-week home exercise program. During each session, CT scans were obtained of the PF joint and quadriceps muscles while a participant was in a supine, nonweight-bearing condition with the knees at full extension. CT images were also acquired targeting the PF joint while a participant was positioned in an upright, weight-bearing condition with the knees at full extension. Participants were assisted in the upright, weight-bearing condition by a custom-built platform that provided a standardized way to position patients in the CT scanner's field of view during the imaging sessions before and after the BoNT-A intervention. The scan parameters for imaging the PF joint and quadriceps muscles under supine, nonweight-bearing conditions were 20 s scan time, 496 frames, and 70 kVp tube voltage. The scan parameters for imaging the PF joint under upright, weight-bearing conditions were 10 s scan time, 248 frames, and 70 kVp tube voltage.

2.5 | Measurement of VL:VM ratio

We measured VL:VM ratio from all participants at baseline and after the BoNT-A and 6-week home exercise program (Figure 1). We used the CT images targeting the quadriceps muscles while a participant was positioned in a supine, nonweight-bearing condition with the knees at full extension. We selected an axial scan plane corresponding to the level of the distal appearance of the rectus femoris muscle. The VL and VM cross-sectional areas were manually outlined, and VL:VM ratio was calculated. All VL:VM ratio measurements were blinded, the image sets were randomized, and the investigator was unaware if an image under analysis was from before or after the intervention. The measurements from each image set were performed twice, on separate days, by the same investigator. Average VL:VM ratio from the two measurements is reported.

2.6 | Measurement of patellar tracking: Patellar tilt and bisect offset

We measured patellar tracking from all participants before and after the BoNT-A injections and 6-week home exercise program.

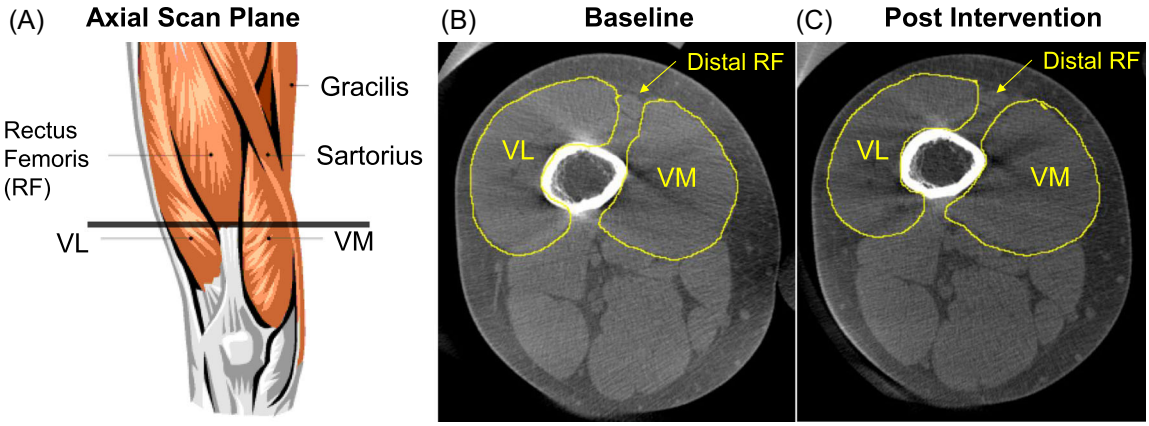

FIGURE 1 Measurement of VL:VM cross-sectional area ratio from CT images targeting the quadriceps muscles while a participant was positioned in a supine, nonweight-bearing condition with the knees at full extension. (A) An axial scan plane (dashed line) corresponding to the level of the distal appearance of the rectus femoris muscle was chosen. The VL and VM cross-sectional areas were manually outlined, and VL:VM ratio was calculated (B) at baseline and (C) after the BoNT-A and 6-week home exercise program. BoNT-A, botulinum neurotoxin type A; CT, computed tomography; VL, vastus lateralis; VM, vastus medialis.

Two-dimensional patellar tracking measures, patellar tilt and bisect offset, were obtained from CT images targeting the PF joint while a participant was positioned in an upright, weight-bearing condition with the knees at full extension. We identified an oblique-axial plane image from the 3D CT volume; this was done to maintain consistency with previous studies.[10,13,37,38] The oblique-axial plane intersected the center of the patella and the most posterior points on the femoral condyles. Anatomical landmarks were identified on the oblique-axial plane image; the landmarks included the most lateral and most medial points on the patella, the most posterior points on the femoral condyles, and the deepest point of the trochlear groove.[10,13] Patellar tilt, defined as the angle between the patella and the posterior femoral condyles, was used to measure patellar internal–external rotation relative to the femur. A more positive tilt angle indicated greater external rotation of the patella relative to the femur. Bisect offset, defined as the percentage of the patella lateral to the midline of the femur, was used to measure the medial–lateral position of the patella relative to the femur.[10,13] A greater bisect offset percentage indicated a more lateral position of the patella relative to the femur. All patellar tilt and bisect offset measurements were performed by a single blinded investigator. The average intraobserver variance between measurements due to the selection of the oblique-axial plane and anatomical landmarks was 2° for patellar tilt and 4% for bisect offset.

2.7 | Anterior Knee Pain Score

We obtained Anterior Knee Pain Score[39] from all participants during initial screening (before BoNT-A injections), immediately after the BoNT-A injections and 6-week home exercise program, and at least 2 years after completing the intervention. The Anterior Knee Pain Score provides a subjective evaluation of a participant's symptoms and functional limitations.[39] The Anterior Knee Pain Score was created with questions about specific activities of daily living related to PF pain and has been previously validated in patients with PF pain.[39] The Anterior Knee Pain Score ranges from a minimum of 0 to a maximum of 100, with a score of 100 indicating no pain or disability. The participants were instructed to complete the questionnaire independently to exclude investigator bias.[39]

2.8 | Classification of participants into maltracking and normal tracking groups

Participants were classified into normal tracking and maltracking groups based on their patellar tilt and bisect offset values obtained from upright, weight-bearing imaging.[10,13,37] We used gender-specific maltracking thresholds because of statistically significant differences in patellar tracking measures between males and females.[10,13,37] The gender-specific maltracking thresholds were 11.8° (males) and 15.4° (females) for patellar tilt, and 68.8% (males) and 72.8% (females) for bisect offset; these values were obtained by averaging the gender-specific maltracking thresholds from previous studies.[10,13,37] A participant was classified as a maltracker if either patellar tilt or bisect offset was greater than the corresponding gender-specific thresholds. Nine (two males, seven females) participants were classified as maltrackers and four (two males, two females) participants were classified as normal trackers.

2.9 | Data analysis and statistical methods

We quantified the effects of the BoNT-A and 6-week home exercise program on VL:VM ratio, patellar tracking, and Anterior Knee Pain Score. Before each statistical comparison, we tested if the data were normally distributed using the Shapiro–Wilk test. If the data passed the normality test, we used *t*-tests. If the data failed normality, we used Wilcoxon signed-rank tests. We chose $p < 0.050$ for testing statistical significance and corrected for multiple comparisons using the Bonferroni correction (i.e., $p < 0.050$ when comparing all PF pain participants, and $p < 0.025$ when comparing PF pain participants classified into maltracking and normal tracking groups). We compared average VL:VM ratios from before and after the BoNT-A injections with home exercises using one-tailed, paired *t*-tests for all PF pain participants and PF pain participants classified into maltracking and normal tracking groups. In addition, we compared average VL and VM cross-sectional areas from before and after the BoNT-A injections with home exercises using one-tailed, paired *t*-tests for all PF pain participants and PF pain participants classified into maltracking and normal tracking groups. Next, we compared average patellar tilt and bisect offset values from before and after the BoNT-A injections with home exercise using one-tailed, paired *t*-tests for all PF pain participants and PF pain participants classified into maltracking and normal tracking groups. We evaluated the relationship between change in patellar tilt and change in bisect offset after BoNT-A injections with home exercises; a linear regression model was used to test for the significance of this relationship ($p < 0.050$).

We performed a one-way repeated measures analysis of variance (ANOVA) to test the effect of BoNT-A injections with home exercises on Anterior Knee Pain Score at two time points (immediately after the intervention and after at least 2 years). We verified that the pain scores were normally distributed for all three time points (before, immediately after, and after 2 years of follow-up). The pain scores failed Mauchly's Test for Sphericity; to address this, we applied a Greenhouse Geisser Correction after the one-way repeated measures ANOVA. Post hoc comparisons were performed using one-tailed paired *t*-tests. We chose $p < 0.050$ for testing significance between the time points and then corrected for multiple comparisons using the Bonferroni correction ($p < 0.017$ for three comparisons: before, immediately after, and after at least 2 years of follow-up). Furthermore, one-tailed *t*-tests are appropriate for our analyses because we can anticipate the directionality of effect post intervention for each of our metrics. We expected VL:VM ratio and VL area to decrease, VM area to increase, patellar tilt and bisect offset values to decrease, and Anterior Knee Pain Score to increase post intervention.

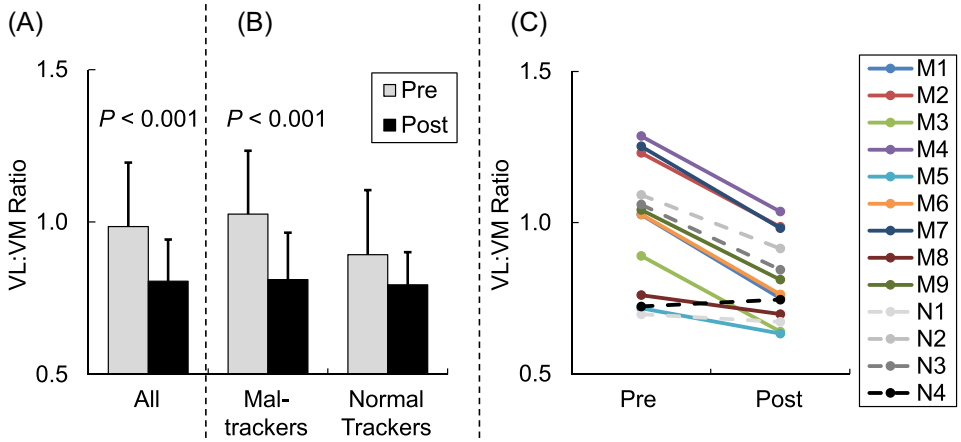

FIGURE 2 Average (+1 SD) VL:VM cross-sectional area ratios from pre and post BoNT-A injections with a 6-week home exercise intervention from (A) all PF pain participants and (B) participants classified into maltracking and normal tracking groups. *p* values are shown for statistically significant differences; $p < 0.050$ in (A), $p < 0.025$ in (B) to correct for multiple comparisons using Bonferroni correction. (C) VL:VM ratios pre and post BoNT-A injections with home exercises from individual participants. BoNT-A, botulinum neurotoxin type A; M, maltrackers, N, normal trackers; SD, standard deviation; VL, vastus lateralis; VM, vastus medialis.

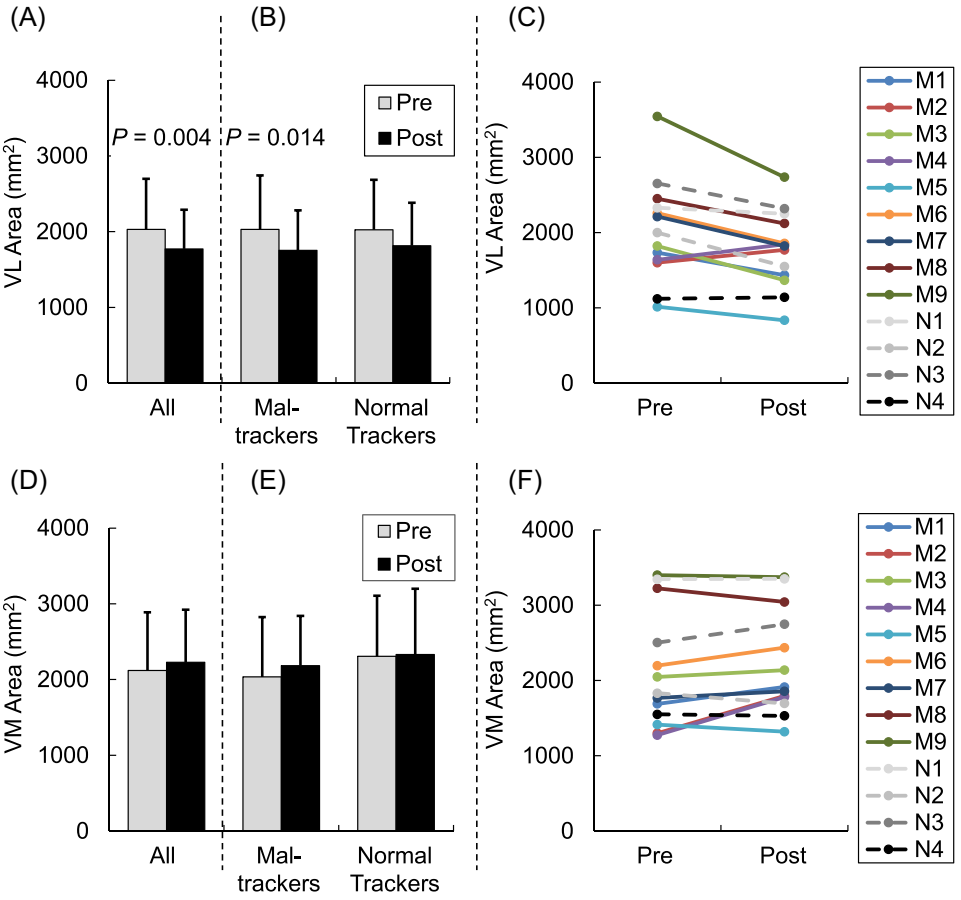

FIGURE 3 Average (+1 SD) vastus lateralis (VL) (A, B) and vastus medialis (VM) (C, D) cross-sectional areas from pre and post BoNT-A injections with a 6-week home exercise intervention from (A, D) all PF pain participants and (B, E) participants classified into maltracking and normal tracking groups. *p* values are shown for statistically significant differences; $p < 0.050$ in (A, D), $p < 0.025$ in (B, E) to correct for multiple comparisons using Bonferroni correction. Cross-sectional areas of the (C) VL and (F) VM muscles pre and post BoNT-A injections with home exercises from individual participants. BoNT-A, botulinum neurotoxin type A; M, maltrackers, N, normal trackers; PF, patellofemoral; SD, standard deviation.

3 | RESULTS

BoNT-A in combination with the 6-week home exercise program reduced VL:VM ratio in patients with chronic PF pain (Figure 2). The average VL:VM ratio from all PF pain participants decreased by 18% after the intervention ($p < 0.001$, Figure 2A). Further classification showed a reduction in VL:VM ratio only in participants classified as maltrackers (21%, $p < 0.001$, Figure 2B). We did not detect a reduction in VL:VM ratio in the four participants classified as normal trackers ($p = 0.093$, Figure 2B), although we observed a reduction in VL:VM ratio in 12 out of 13 participants (Figure 2C).

The reduction in VL:VM ratio was primarily due to reduction in VL cross-sectional area after the intervention (Figure 3). Average VL cross-sectional area from all PF pain participants was 13% lower after the intervention ($p = 0.004$, Figure 3A). Further classification showed a decrease in in VL cross-sectional area in participants classified as maltrackers (14%, $p = 0.014$, Figure 3B); we did not detect a reduction in VL cross-sectional area in the participants classified as normal trackers ($p = 0.125$, Figure 3B). We observed a reduction in VL cross-sectional area in 10 out of 13 participants (Figure 3C). Our statistical tests did not reveal a significant increase in VM cross-sectional area after the intervention in all PF pain participants ($p = 0.095$, Figure 3D), participants classified as maltrackers ($p = 0.082$, Figure 3E), or participants classified as normal trackers ($p = 0.563$, Figure 3E).

BoNT-A in combination with the 6-week home exercise program reduced lateral patellar tracking in patients with chronic PF pain (Figure 4). Average patellar tilt and bisect offset values from all PF pain participants decreased by 19% ($p = 0.020$, Figure 4A) and 5% ($p = 0.025$, Figure 4D), respectively, after the intervention. Further classification showed reductions in patellar tilt (26%, $p = 0.001$, Figure 4B) and bisect offset (8%, $p = 0.014$, Figure 4E) in participants classified as maltrackers. We did not detect a change in patellar tilt ($p = 0.874$, Figure 4B) or bisect offset ($p = 0.438$, Figure 4E) in participants classified as normal trackers. We observed reductions in patellar tilt and bisect offset in 11/13 (Figure 4C) and 10/13 (Figure 4F) participants, respectively. Change in bisect offset

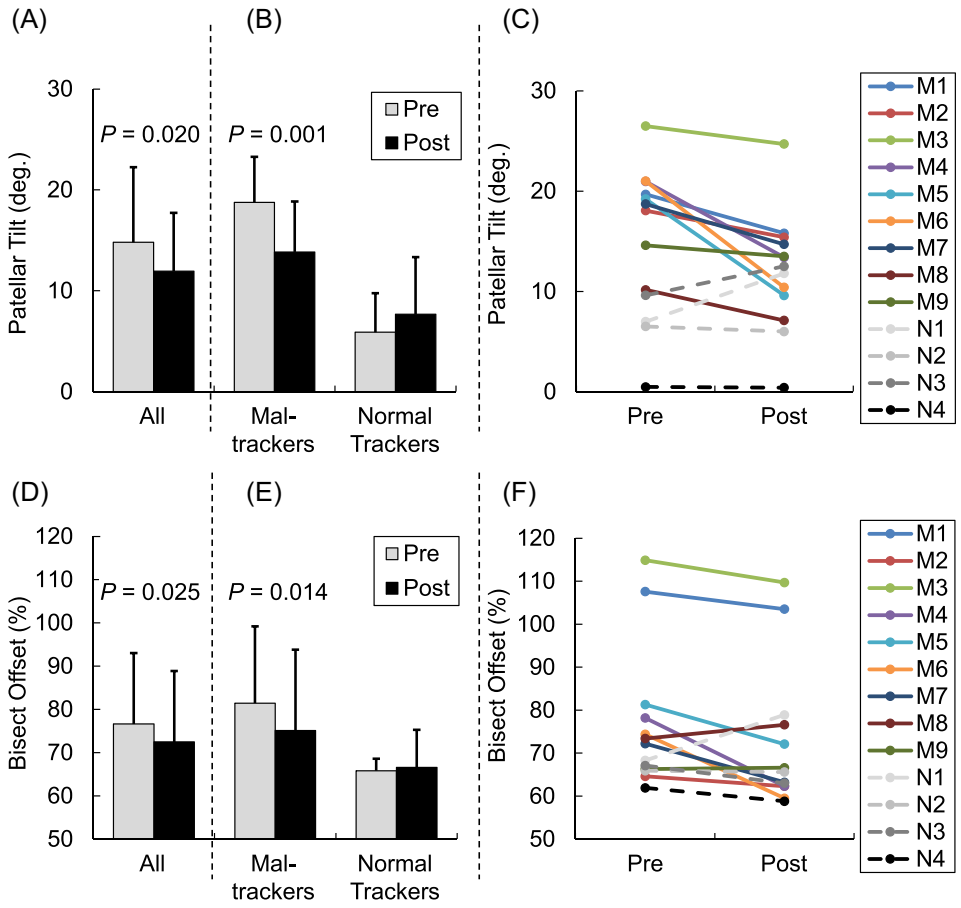

FIGURE 4 Average (+1 SD) patellar tilt (A, B) and bisect offset (C, D) values from pre and post BoNT-A injections with a 6-week home exercise intervention from (A, D) all PF pain participants and (B, E) participants classified into maltracking and normal tracking groups. p values are shown for statistically significant differences; $p < 0.050$ in (A, D), $p < 0.025$ in (B, E) to correct for multiple comparisons using Bonferroni correction. (C) Patellar tilt and (F) bisect offset values pre and post BoNT-A injections with home exercises from individual participants. BoNT-A, botulinum neurotoxin type A; M, maltrackers, N, normal trackers; PF, patellofemoral; SD, standard deviation.

was associated with change in patellar tilt ($R^2 = 0.650$, $p < 0.001$, Figure 5). Four participants classified as maltrackers before the intervention transitioned to normal tracking after the intervention (Figure 5).

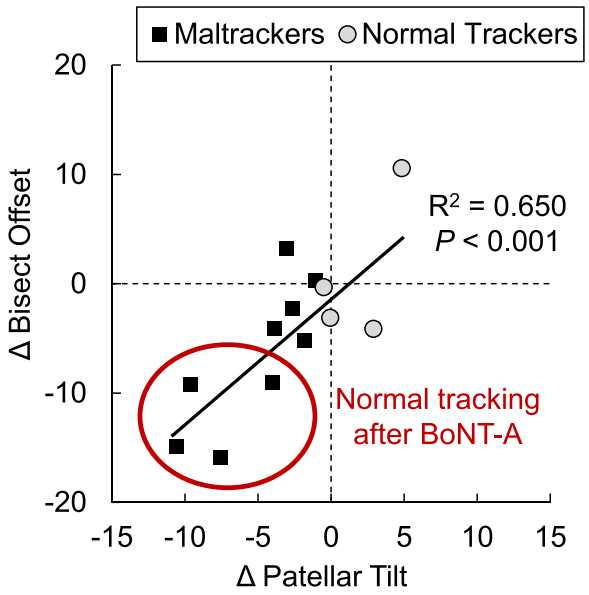

FIGURE 5 Relationship between change in patellar tilt and change in bisect offset after the BoNT-A injections with a 6-week home exercise intervention in PF pain participants classified as maltrackers and normal trackers. The regression line represents a significant relationship ($R^2 = 0.650$, $p < 0.001$) in all participants. Four participants classified as maltrackers transitioned to normal tracking after the intervention. BoNT-A, botulinum neurotoxin type A; PF, patellofemoral.

BoNT-A injections in combination with the 6-week home exercise program improved Anterior Knee Pain Scores immediately after the intervention; these scores remained improved for at least 2 years of follow-up (Figure 6). The one-way repeated measures ANOVA produced a significant effect at the two time points after the intervention ($F(2, 22) = 9.86$, $p = 0.004$, after Greenhouse Geisser correction for sphericity). Post hoc comparisons yielded average Anterior Knee Pain Scores that were 13% ($p < 0.001$) and 12% ($p = 0.011$) greater immediately after intervention and at 2-year follow-up, respectively, compared to pre-intervention pain scores (Figure 6A). We found no difference in pain scores between immediately after the intervention and at the 2-year follow-up ($p = 0.361$, Figure 6A). We observed improvements in Anterior Knee Pain Scores in 11/13 participants immediately after intervention, and scores remained improved in 9/12 participants at 2-year follow-up (Figure 6B).

We found no association between the change in VL:VM ratio and the change in patellar tilt after the intervention ($R^2 = 0.116$, $p = 0.256$, Figure 7A). We found no association between change in VL:VM ratio and change in bisect offset after the intervention ($R^2 = 0.285$, $p = 0.060$, Figure 7B) and no association between change in VL:VM ratio and change in pain score after the intervention ($R^2 = 0.168$, $p = 0.163$, Figure 7C).

4 | DISCUSSION

The purpose of this study was to quantify the effects of BoNT-A injections on vasti muscle size, patellar tracking, and pain in chronic PF pain patients. All participants failed to respond to conservative treatment, including at least 6 weeks of supervised physical therapy

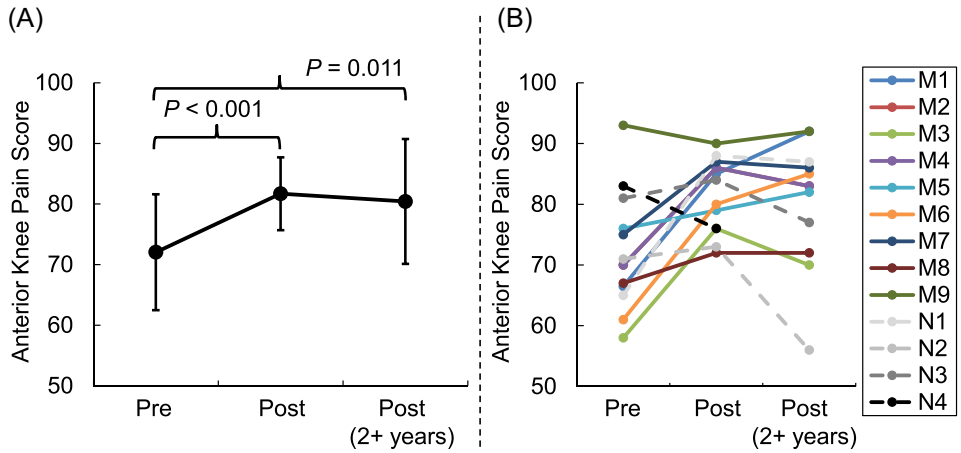

FIGURE 6 Average (±1 SD) self-reported anterior knee pain scores from pre, post, and post 2+ years BoNT-A injections with a 6-week home exercise intervention from all PF pain participants, (A) A one-way repeated measures ANOVA produced a significant effect at the two time points post intervention ($F(2, 22) = 9.86$, $p = 0.004$ after Greenhouse Geisser correction for sphericity). p Values for post hoc paired samples t-tests are shown for statistically significant differences; $p < 0.017$ (0.050/3) to correct for multiple comparisons using Bonferroni correction. (B) Anterior Knee Pain Scores from pre, post, and post 2+ years BoNT-A injections with home exercises from individual participants. ANOVA, analysis of variance; BoNT-A, botulinum neurotoxin type A; *M*, Maltrackers, *N*, Normal Trackers; PF, patellofemoral; SD, standard deviation.

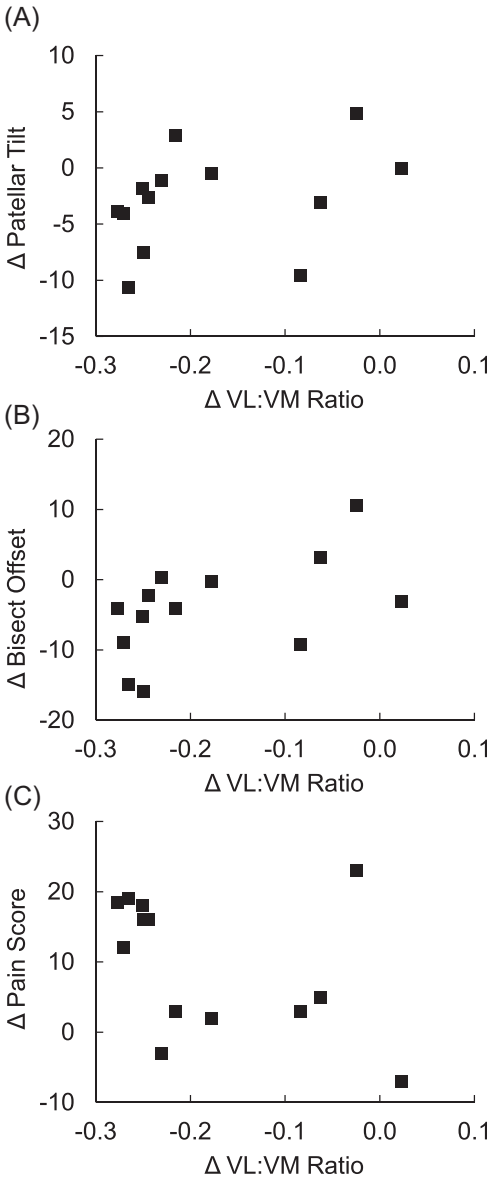

FIGURE 7 Relationship between change in VL:VM ratio and (A) change in patellar tilt, (B) change in bisect offset, and (C) change in pain score after the BoNT-A injections with a 6-week home exercise intervention. No relationship was statistically significant. BoNT-A, botulinum neurotoxin type A; VL, vastus lateralis; VM, vastus medialis.

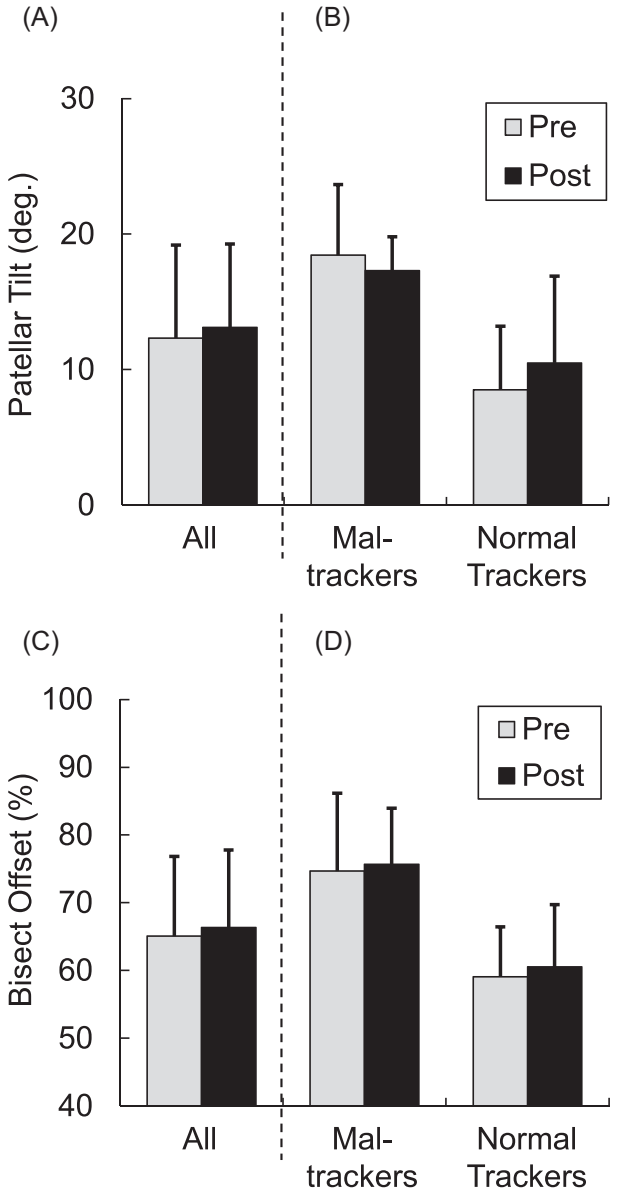

FIGURE 8 Average (+1 SD) patellar tilt (A, B) and bisect offset (C, D) values from supine, nonweight-bearing scans obtained pre and post BoNT-A injections with a 6-week home exercise intervention from (A, C) all PF pain participants and (C, D) participants classified into maltracking and normal tracking groups. BoNT-A, botulinum neurotoxin type A; PF, patellofemoral; SD, standard deviation.

focused on hip and quadriceps muscle strengthening exercises. Our first hypothesis, that BoNT-A injections in combination with a 6-week home exercise program would reduce VL:VM cross-sectional area ratio, was supported. The average VL:VM ratio decreased by 18% after the intervention (Figure 2A) and was reduced in 12/13 participants (Figure 2C). Our second hypothesis, that BoNT-A injections in combination with a 6-week home exercise program would reduce lateral patellar tracking, was also supported. The average patellar tilt and bisect offset decreased by 19% (Figure 4A) and 5% (Figure 4D), respectively, after the intervention. We observed improvements in patellar tilt in 11/13 participants (Figure 4C) and bisect offset in 10/13 participants (Figure 4F). In support of our third hypothesis, that BoNT-A injections in combination with a 6-week home exercise program would improve functional pain score, the average Anterior Knee Pain Score improved by 13% immediately after intervention and remained improved for at least 2 years after the intervention (Figure 6).

This study provides new evidence that supports the use of BoNT-A injections for treating an underlying mechanism of PF pain, namely excessive lateral tracking of the patella due to an imbalance in the vasti muscles. Although prior studies have reported

TABLE 2 Power of comparisons pre and post BoNT-A injections with a 6-week home exercise intervention from all PF pain participants and participants classified into maltracking and normal tracking groups

	All (n = 13)	Maltrackers (n = 9)	Normal Trackers (n = 4)
VL:VM ratio	92%[a]	93%[a]	21%
VL area	40%	31%	13%
VM area	13%	14%	5%
Patellar tilt	41%	87%[a]	14%
Bisect offset	21%	23%	7%
Anterior Knee Pain Score (post 6 weeks)	98%[a]	97%[a]	27%
Anterior Knee Pain Score (post 2 years)	87%[a]	97%[a]	7%

Abbreviations: BoNT-A, botulinum neurotoxin type A; PF, patellofemoral; VL, vastus lateralis; VM, vastus medialis

[a]denotes the comparisons that met the minimum threshold of 80% power.

improvements in PF pain following a BoNT-A intervention,[32–35] evidence that BoNT-A injections improve the balance of cross-sectional areas of the VL and VM and lateral patellar tracking is limited. One previous study by Singer et al.[32] reported reduction in VL:VM activation ratio following a BoNT-A intervention, where VL:VM activation ratio was calculated from electromyography data.[32] In our study, we calculated VL:VM cross-sectional area ratio from CT imaging, a more direct measure for quantifying changes in the VL and VM muscle sizes following the intervention. Our results also demonstrate that a combination of BoNT-A injections and home exercise reduced patellar tilt and bisect offset in most participants. Indeed, four participants classified as maltrackers before the intervention transitioned to normal tracking after the intervention (Figure 5).

Our results support previous studies that emphasize the importance of measuring lateral patellar maltracking under a weight-bearing condition.[10,13,37] Our results showed reductions in patellar tracking due to the BoNT-A injections with a home exercise intervention only when participants were examined in an upright, weight-bearing condition. We repeated our analyses by classifying our participants into maltracking and normal tracking groups from CT imaging from supine, nonweight-bearing condition; these results showed no reduction in patellar tilt or bisect offset after the BoNT-A injection and home exercise intervention (Figure 8). This highlights the importance of accurately determining patellar tracking under a weight-bearing condition.[10,13,37]

It is difficult to address directly the influence of VM weakness on PF biomechanics and pain from our data. Previous studies have reported that VM weakness causes excessive lateral tracking of the patella, leading to pain.[40–43] The results of our study showed that a combination of BoNT-A injections and home exercise program reduced VL:VM ratio (Figure 2), but this reduction was primarily due to reduction in VL cross-sectional area after the intervention (Figure 3A–C). We observed no increase in VM cross-sectional area after the intervention (Figure 3D–F). As such, we are unable to conclude that our observed improvements in patellar tracking measures and pain scores were due to increased VM strength.

A limitation of this study is our sample size of 13 PF pain participants. Eighteen participants were injected with BoNT-A, but only 13 participants completed the 6-week home exercise program, CT imaging, and pain score questionnaire immediately after the intervention. Due to our small sample size, our statistical power did not meet the minimum threshold of 80% for all our comparisons (Table 2). Comparisons of the outcome measures separately for the maltracking and normal tracking groups provide an intuitive approach to determine the subset of participants who will most benefit from a BoNT-A intervention, that is, the participants classified as maltrackers. Indeed, the four participants whose patellar tracking measures improved the most were all classified as maltrackers (Figure 5). A larger trial with more participants is required to validate the findings of this study. A second limitation is that our study did not include a placebo group. Singer et al.[32] reported significantly greater improvements in pain scores and VL:VM activation ratio in patients injected with BoNT-A compared to patients injected with a placebo; however, changes in VL:VM cross-sectional area ratio and patellar tracking in patients injected with BoNT-A compared to patients injected with a placebo remain unclear.

Accurate determination of patellar maltracking under weight-bearing conditions is challenging using current clinical techniques. Patellar maltracking is usually determined during clinical assessment in supine or seated positions, with minimal loading of the PF joint.[44] Unloaded conditions do not represent the load-bearing tasks that elicit pain, and patellar maltracking measured under such conditions may not replicate patellar motion during weight-bearing activities.[45] Our results show that diagnosis of patellar maltracking from nonweight-bearing condition may lead to inaccurate diagnosis of the underlying mechanism of pain, and inaccurate assessment of treatment pathways such as a BoNT-A intervention. Accurate classification of PF pain patients under weight-bearing condition may identify individuals who will most benefit from a BoNT-A intervention.

In conclusion, this study provides new evidence in support of BoNT-A for the treatment of PF pain in patients who have failed conservative pathways. Classification of patients under weight-bearing condition may identify individuals who will most benefit from a BoNT-A treatment.

AUTHOR CONTRIBUTIONS

All authors contributed immensely at all stages of this research, and are intimately familiar with the methods and findings reported in this manuscript. Saikat Pal drafted the initial version of the manuscript. Saikat Pal and Jang-Hwan Choi were responsible for the acquisition of data and all data analysis. Michael Fredericson performed all clinical evaluations and botulinum neurotoxin injections. Michael Fredericson and Scott L. Delp made large contributions to the revisions of the manuscript. Saikat Pal, Michael Fredericson, and Scott L. Delp are responsible for the concept of the study design. All the authors have read the final manuscript and given their final approval for the manuscript to be published.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

Institutional Review Board approval was granted for this study.

ORCID

Saikat Pal http://orcid.org/0000-0002-6908-5896
Jang-Hwan Choi http://orcid.org/0000-0001-9273-034X

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