Changes in pain profile of patients with haemophilia during 1-year follow-up

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Abstract
Introduction: Patients with haemophilia (PwH) may experience increased sensitivity to pain. Based on the assessment of the somatosensory system, a recent study showed a specific pain profile in PwH when compared to controls by using Quantitative Sensory Testing (QST).

Aim: This study aimed to evaluate the pain profile of affected joints (knee or ankle joints) and a non-affected site (dominant hand) in adult PwH over a 1-year period.

Methods: Twenty-four PwH (severe haemophilia A = 19, B = 3; moderate haemophilia A = 1, B = 1; age: 52±8 years) and 21 healthy controls (age: 52±12 years) were examined by QST. Both knee or ankle joints and the hand as reference were examined twice with an interval of 1 year in order to assess several detection (DT) and pain thresholds (PT).

Results: Statistically significant altered mechanical (P < .001) and pressure (P < .05) PT were found at affected joints and at a non-affected site in PwH when compared to controls. Mechanical DT showed a significant increase at all assessed sites (e.g., at ankle joints PwH vs. controls at baseline/follow up in mN: 13.9±9.8 vs. 12.0±8.2/19.4±12.4 vs. 13.7±11.1; P < .01) in both cohorts. Nevertheless, changes in most parameters within 1 year occurred similarly in both groups.

Conclusion: The statistically significant different QST profile between PwH and controls does not seem to deteriorate further over the course of the year. Thus, under prophylactic treatment, the existing difference in the pain profile between PwH and controls at baseline does not appear to be a progressive process within 1 year.

Keywords
ankle, haemophilia, haemophilic arthropathy, knee, pain, QST, rare disease

1 | INTRODUCTION

Haemophilia is a genetic disorder, inherited in an x-linked recessive trait and characterised by deficiency of coagulation factor VIII (Haemophilia A) or IX (Haemophilia B). This causes an increased number of bleeding events with a tendency for patients to bleed spontaneously in joints, which most often affect elbows, knees, and ankles. These intra-articular bleedings are often accompanied by pain. The knowledge about pain in patients with haemophilia (PwH) is very restricted and mostly assessed by visual analogue scales or pain questionnaires. However, neither method is able to shed light on pain mechanisms in PwH and one might suspect that these methods are inappropriate to assess the pain condition comprehensively.

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In a first study, we showed that pain thresholds are altered in PwH. By doing so, we were able to determine a reduced pressure pain threshold at knee and elbow joints of PwH in comparison to control subjects. This was not observed across reference points such as forehead and sternum. In a subsequent study, which was supported by the clinical research grant program of the World Federation of Haemophilia (WFH), we detected a haemophilic-specific pain profile in PwH. As a result, alterations of the somatosensory system across both affected (the knees) and unaffected landmarks (the hand) in PwH were assessed for the first time. In particular, altered thermal and mechanical detection and pressure pain thresholds were determined in PwH when compared to healthy controls.

Based on the cross-sectional findings of a modified somatosensory system, it was not possible to determine the range of prevailing alterations in the pain condition caused by specific changes of progressing haemophilic arthropathy. Thus, this study aimed to assess changes in pain in knee as well as ankle joints, and also over a 1-year period, in comparison with healthy controls.

2 | MATERIALS AND METHODS

2.1 | Participants

Initially, 58 people were enrolled for the study (PwH: n = 30; controls: n = 28). After reviewing the inclusion and exclusion criteria, 27 PwH and 24 controls were included in the study. 24 PwH and 21 controls participated in the follow-up assessment, so only the results of these persons were considered for final statistical analysis. All patients with severe haemophilia received prophylactic treatment with standard half-life products. Included in the study were patients with moderate to severe haemophilia with at least one painful knee or ankle joint and without inhibitor history, and healthy control subjects, both aged 18 years and older. Exclusion criteria of this study were acute or chronic pain conditions (only controls), regular pain medication (only controls), use of any medication in the 24 h before examinations, and any kind of diseases influencing the somatosensory profile (e.g., neuropathies, dementia, depression, multiple sclerosis). In addition, participants were excluded if they experienced bleeding events (only PwH) in the 2 weeks before the examination date, or had any surgeries 6 months before study inclusion or during the 1-year follow-up period. In total, QST results of n = 45 hands (PwH n = 24; controls n = 21), n = 61 ankle joints (PwH n = 31, controls n = 30), and n = 21 knee joints (PwH n = 10, controls n = 11) were thus analysed.

All examinations that took place at the Department of Sports Medicine or at patient events were performed by the same experienced examiner. The examinations all took place in a quiet room and lasted about 2 h in total. Throughout the procedure, participants lay in a comfortable supine position on a treatment bench.

This study was conducted in accordance with the principles of good clinical and ethical practice and was approved by the ethics committee of the University of Wuppertal. Along with the Declaration of Helsinki, all participants gave written informed consent after being informed about the study’s protocol.

2.2 | Quantitative sensory testing

The ankle or knee joint determined by the most painful joint subjectively perceived within the last 6 months of PwH were examined by the Quantitative Sensory Testing (QST) (see Figure 1). The measurement site at each joint was the medial joint space (knee) or...
lateral joint space (ankle joints). Likewise, the contralateral joint as well as the dominant hand (thenar eminence) were assessed as points of reference. Based on age, matched pairs were formed between PwH and controls. Depending on the joints examined in each PwH, either the knee or ankle joints and the dominant hand were also examined in the corresponding control.

2.3 | Thermal detection thresholds and thermal pain thresholds

The Thermal Sensory Analyzer II (TSA 2001-II, Medoc Ltd., Ramat Yishai, Israel) was used for the assessment. For all thermal thresholds, the participants gave feedback by pressing the button of a response unit. Starting at 32°C, the temperature changed at a rate of 1°C per second for all thermal tests.

To determine the perception thresholds and thermal sensory limen, participants were instructed to press the button as soon as a change in temperature was felt. The thermal sensory limen was calculated by subtracting the arithmetic mean of three cold detection threshold from the arithmetic mean of the three warm detection threshold, measured by three runs. For the thermal pain thresholds, participants gave feedback as soon as pain was felt.

2.4 | Mechanical detection threshold

For the mechanical detection threshold, a set of Frey filaments (.25 mN to 512 mN, OptiHair2-Set, Marstock Nervtest, Germany) was used. The filaments were applied in decreasing intensity until the stimulus was no longer perceived. The application sequence was then reversed until the person again felt the stimulus.

2.5 | Mechanical pain threshold

A set of standardized needle stimulators (Pinprick, MRC Systems GmbH, Germany) was used to determine the mechanical pain threshold. The needles had a blunt contact area of .2 mm with a stimulation intensity of 8, 16, 32, 64, 128, 256, and 512 mN. In ascending intensity, the needles were placed on the skin with a contact time of about 2 s until the person perceived the touch as pointy/sharp. The needles were then applied in descending order until the stimulus was perceived as dull.

2.6 | Mechanical pain sensitivity

The mechanical pain sensitivity was measured via the stimulus-response pattern. In addition to the pinpricks described above, three light tactile stimuli were used with a standardized brush (≈ 200–400 mN; Somedic, Sweden), a cotton swab (≈ 100 mN), and a cotton ball (≈ 3 mN). The subjects were asked to rate the perception of each stimulus on a numerical rating scale from 0 (no pain) to 100 (maximum imaginable pain).

2.7 | Wind-up ratio

The wind-up ratio was determined by comparing the pain rating of a single stimulus with the rating of a series of 10 stimuli applied repetitively every second. A needle stimulus with a weight force of 256 mN was applied and the numerical evaluation scale from 0 to 100 was used. The wind-up ratio was calculated by dividing the mean pain ratings of repeated stimulus intensity by the mean of the single pinprick stimulus.

2.8 | Vibration detection threshold

A Rydel-Seiffer tuning fork was used to determine the vibration threshold. The vibrating tuning fork was placed on a bony site. The participants were instructed to indicate the moment at which the vibration was no longer felt.

2.9 | Pressure pain threshold

The pressure pain threshold was determined by means of a pressure algometer (FPX-25, Wagner Instruments, Greenwich, CT, USA). The force was continuously increased with a ramp of 10 N/s until a painful sensation was felt for the first time.

| Parameter | PwH | Con | P-value |
|-----------|-----|-----|---------|
| Age (years) | 52 ± 8 (34-70) | 52 ± 12 (29-66) | .769 |
| Height (m) | 1.79 ± .07 (1.63-1.98) | 1.82 ± .07 (1.67-1.94) | .188 |
| Weight (kg) | 81.2 ± 12.2 (53.0-103.0) | 85.2 ± 12.4 (68.0-123.0) | .368 |
| Type of haemophilia n (%) | Severe A: 19 (79) | Severe B: 3 (11) | Moderate A: 1 (4) | Moderate B: 1 (4) | – | – |
| Treatment regime | Prophylactic: 22 (92) | On demand: 2 (8) |
| HIV n % | Yes: 19 (70) | Yes: 0 (0) | None: 8 (30) | None: 24 (100) | – |
| Hepatitis n % | C: 4 (15) | A & C: 1 (4) | B & C: 3 (11) | A & B & C: 1 (4) | None: 18 (66) |

Data are presented as mean ± standard deviation or as total number (%).
2.10 Joint status

The status of knee and ankle joints were examined using the Physical Joint Examination instrument—described by Gilbert and recommended by the Orthopedic Advisory Committee of the World Federation of Haemophilia (WFH)—to compare these data with previous study results. Higher score points imply an increased deficit in the functional and structural joint status, with a maximum possible value of 12 score points for each joint. The subjective pain condition was evaluated using the pain sub-score of the WFH physical examination. By doing so, each joint was given a potential score from 0 (no pain) to 3 (severe pain) points. In addition, the subjective pain intensity was recorded using the numeric rating scale (0 = no pain to 10 = maximum imaginable pain) for each joint examined.

2.11 Data evaluation and statistical analysis

Evaluation of the QST parameters was performed as recommended by the DFNS (Deutscher Forschungsverbund Neuropathischer Schmerzen) protocol. Therefore, all parameters except cold pain thresholds, heat pain thresholds, paradox heat sensations, and vibration detection thresholds were log10-transformed in order to achieve a log-normal distribution. For pain ratings of mechanical pain sensitivity, a constant of 0.1 was added before log-transformation in order to avoid a loss of zero-ratings. Data from the left and right sides of the body were combined for further analysis. Thereafter, QST results of each test site were analysed using repeated-measures analysis of variance with "time" as within-group factor and "group" as between-subject factor.

### TABLE 2 Joint and pain status of patients with haemophilia (PwH) (n = 24) and healthy controls (Con) (n = 21)

| Parameter          | Group | T0     | T1     | p value T0 vs T1 | p value PwH vs Con |
|--------------------|-------|--------|--------|------------------|--------------------|
| **WFH pe score**   |       |        |        |                  |                    |
| Ankle joint left   | PwH   | 6.5 ± 1.9 | 5.2 ± 2.7 | .035             | .000 .000          |
|                    | Con   | 1.5 ± 0.7  | 2.0 ± 1.1  | .151             |                    |
| Ankle joint right  | PwH   | 6.2 ± 2.2  | 4.6 ± 1.8  | .179             | .000 .000          |
|                    | Con   | 1.4 ± 0.8  | 1.8 ± 1.0  | .346             |                    |
| Knee joint left    | PwH   | 4.2 ± 2.1  | 4.2 ± 2.3  | .873             | .000 .000          |
|                    | Con   | 1.3 ± 0.8  | .8 ± 0.8   | .021             |                    |
| Knee joint right   | PwH   | 5.0 ± 2.7  | 4.3 ± 2.3  | .439             | .000 .000          |
|                    | Con   | 1.5 ± 1.0  | .7 ± 0.9   | .003             |                    |
| **WFH pain score** |       |        |        |                  |                    |
| Ankle joint left   | PwH   | 1.1 ± 1.1  | 1.0 ± 1.2  | .416             | .000 .000          |
|                    | Con   | .0 ± 0.0   | .0 ± 0.0   | 1.000            |                    |
| Ankle joint right  | PwH   | 1.1 ± 1.1  | 1.2 ± 1.3  | .884             | .000 .000          |
|                    | Con   | .0 ± 0.2   | .0 ± 0.2   | 1.000            |                    |
| Knee joint left    | PwH   | .6 ± 1.0   | .4 ± 0.8   | .700             | .002 .039          |
|                    | Con   | .0 ± 0.0   | .0 ± 0.2   | .810             |                    |
| Knee joint right   | PwH   | .6 ± .9    | .6 ± .9    | .964             | .033 .001          |
|                    | Con   | .2 ± .6    | .0 ± .0    | .643             |                    |
| **NRS**            |       |        |        |                  |                    |
| Ankle joint left   | PwH   | 2.0 ± 2.3  | 1.3 ± 1.7  | .292             | .000 .000          |
|                    | Con   | .0 ± 0.0   | .0 ± 0.0   | 1.000            |                    |
| Ankle joint right  | PwH   | 2.0 ± 2.1  | 1.5 ± 1.9  | .373             | .000 .000          |
|                    | Con   | .1 ± 0.4   | .0 ± 0.0   | .731             |                    |
| Knee joint left    | PwH   | .7 ± 1.1   | .5 ± 0.9   | .630             | .002 .045          |
|                    | Con   | .0 ± 0.0   | .1 ± 0.4   | .713             | .002 .045          |
| Knee joint right   | PwH   | .8 ± 1.2   | .8 ± 1.3   | .937             | .023 .001          |
|                    | Con   | .1 ± 0.5   | .0 ± 0.0   | .810             |                    |

Results based on n = 61 ankle joints (PwH n = 31, controls n = 30), and n = 21 knee joints (PwH n = 10, controls n = 11).

Abbreviations: WFH, World Federation of Haemophilia; pe score, physical examination score; NRS, numeric rating scale.
Furthermore, QST profiles were created to compare the results of PwH and controls. Each parameter was Z-transformed to achieve a comparison between the values of both groups independent of the different units of each parameter. Z-transformation was performed for each parameter using the following expression:

$$Z\text{-score} = \frac{\text{value single patient} - \text{mean controls}}{\text{standard deviation controls}}$$

Results of baseline and follow-up assessments were also compared by means of Z-transformation:

$$Z\text{-score} = \frac{\text{value follow-up} - \text{mean baseline}}{\text{standard deviation baseline}}$$

Comparisons of clinical and anthropometric data between PwH and controls were performed using the Mann–Whitney U test. Wilcoxon rank tests were conducted to analyse the clinical data in a longitudinal section. The significance level (alpha) for all tests was set at $P \leq .05$. All statistical analyses were performed using the Statistical Package for the Social Sciences version 25 software program (IBM Corp., Armonk, NY, USA) for Macintosh.

3 | RESULTS

The anthropometric and clinical data of the two groups studied are shown in Table 1 and Table 2, respectively. PwH showed statistically significant higher joint scores both at study entry and at follow-up. Likewise, the PwH pain scores and pain intensities at both points in time were statistically significantly higher in all examined joints than in the controls (see Table 2).

General statistically significant group differences between PwH and controls were found for both DT and PT at all three examined sites. Mechanical as well as pressure PT were statistically significantly reduced at both knees, ankles, and the hand in PwH when compared to controls (mechanical PT: $P < .001$; pressure PT: $P < .05$). Pain sensitivity to mechanical stimuli was statistically significantly increased at the knee joints in PwH ($P = .028$), whereas at the ankle joints there was only a trend for hyperalgesia ($P = .086$). In contrast, there was no difference between the two groups for these stimuli at the hand ($P = .413$) (see Tables 3–5).

Analysing the QST results by ANOVA with the factors time*group separately for each test point revealed statistically significant alterations in the pain profile of PwH and controls during the 1-year course. For example, in both PwH and controls, the mechanical DT showed a statistically significant increase at the knee joints (PwH vs. controls at baseline/follow up in mN: $6.8 \pm 6.9$ vs. $4.7 \pm 2.3/9.8 \pm 6.1$ vs. $6.8 \pm 7.3$; $P < .001$), ankle joints (PwH vs. controls at baseline/follow up in mN: $13.9 \pm 19.8$ vs. $12.0 \pm 8.2/19.4 \pm 12.4$ vs. $13.7 \pm 11.1$; $P < .01$) and the dominant hand (PwH vs. controls at baseline/follow up in mN: $1.7 \pm 1.2$ vs. $1.9 \pm 1.3/3.8 \pm 7.7$ vs. $2.6 \pm 5.1$; $P < .001$) between the two examinations, with larger changes in the patient group. In contrast, the factors time*group analyses showed no relevant changes for the thermal DT ($P > .05$) (see Tables 3–5).

Raw data of QST measurements were subsequently analysed by Z-transformation. Using this method, the differences between PwH and controls, as well as relevant changes in the somatosensory profile over the course of 1 year of PwH and controls, were compared graphically. By doing so, it could be demonstrated that the alterations of most QST parameters within 1 year are approximately similar for PwH and controls (see Figures 2–4).

4 | DISCUSSION

Using the QST data, we were able to demonstrate for the first time a pain profile of the ankle joints, and also the course of pain at knee joints, ankle joints, and an unaffected reference over 1 year in PwH using semi-objective pain measurements. Thus, it has been shown that

| Parameter | Group | T0     | T1     | ANOVA | PwH vs Con |
|-----------|-------|--------|--------|-------|------------|
| CDT (Δ°C) | PwH   | -2.1 ± 1.2 | -1.9 ± 1.3 | .356  | .652       |
|           | Con    | -1.7 ± .8   | -1.8 ± .8   |       |            |
| WDT (Δ°C) | PwH   | 4.4 ± 3.7   | 4.4 ± 3.1   | .053  | .397       |
|           | Con    | 3.5 ± 1.4   | 2.1 ± 1.3   |       |            |
| TSL (Δ°C) | PwH   | 6.6 ± 3.3   | 7.9 ± 4.3   | .294  | .721       |
|           | Con    | 5.8 ± 2.3   | 6.5 ± 2.4   |       |            |
| CPT (°C)  | PwH   | 7.2 ± 15.3  | 15.4 ± 10.6 | .199  | .212       |
|           | Con    | 5.3 ± 10.9  | 9.9 ± 11.0  |       |            |
| HPT (°C)  | PwH   | 43.3 ± 4.5  | 44.0 ± 3.4  | .049  | .036       |
|           | Con    | 47.3 ± 1.7  | 44.5 ± 2.8  |       |            |
| MPS (mN)  | PwH   | 7.2 ± 7.8   | 7.4 ± 5.6   | .029  | .028       |
|           | Con    | 6.4 ± 4.9   | 4.4 ± 3.6   |       |            |
| MDT (mN)  | PwH   | 6.8 ± 6.9   | 9.8 ± 6.1   | .000  | .012       |
|           | Con    | 4.7 ± 2.3   | 6.8 ± 7.3   |       |            |
| MPT (NRS) | PwH   | 25.7 ± 19.7 | 32.7 ± 33.7 | .001  | .000       |
|           | Con    | 51.1 ± 38.3 | 61.9 ± 68.2 |       |            |
| WUR (NRS) | PwH   | 3.7 ± 2.4   | 3.8 ± 2.7   | .040  | .915       |
|           | Con    | 2.1 ± 1.2   | 3.8 ± 4.1   |       |            |
| VDT (x/8) | PwH   | 6.0 ± 1.9   | 6.1 ± 2.2   | .871  | .781       |
|           | Con    | 6.2 ± 1.1   | 6.4 ± .9    |       |            |
| PPT (N)   | PwH   | 40.5 ± 13.1 | 36.7 ± 14.5 | .164  | .000       |
|           | Con    | 98.2 ± 27.0 | 82.1 ± 26.1 |       |            |

Results based on $n = 21$ knee joints (PwH $n = 10$, controls $n = 11$). Abbreviations: CDT, cold detection threshold; WDT, warmth detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold.
significant changes in the somatosensory profile exist in the ankle joints of PwH compared to healthy controls. Furthermore, it became apparent that the existing differences in the pain profile do not spread further with a prophylactic therapy regimen over 1 year.

Compared to the previous published QST data for the knee joints, 7 the PwH in this study showed an even more pronounced mechanical hyperalgesia at the test site. While in the previous data only mechanical hyperalgesia based on the pressure pain threshold was observed, in this study, the entire range of pain parameters for mechanical stimuli demonstrates hyperalgesia in PwH (see Tables 3–5). We can only speculate about possible reasons for these differences between the older and newer data of PwH. For example, the duration of pain exposure or the intensity of the pain could lead to different adjustments in the somatosensory profile. In osteoarthritis, these two factors influencing the sensitisation process could be proven and should also be urgently analysed in PwH in order to better understand the development and maintenance of pain. 11

The pain profile of ankle joints of PwH showed a very similar pattern to that of the knee joints. Mechanical hyperalgesia could also be demonstrated for ankle joints based on the statistically significant differences in pressure PT and mechanical pain sensitivity between PwH and controls. In addition, the hands of PwH, as a non-affected reference, also showed statistically significant alterations for painful PT compared to healthy controls, secondary hyperalgesia was also detected. This finding further supports the evidence to date that not only peripheral sensitisation, but also sensitisation of the central pain-processing system can be found in PwH. 7,12,13 It can be assumed that this hyperalgesia was induced by peripheral inflammatory processes. The prolonged stimulation of the nociceptors, therefore, caused the stimulation threshold to be lowered, leading to central sensitisation and triggering a painful sensation by a previously non-painful stimulus. In patients with osteoarthritis, prolonged and intense nociceptive input has been identified as an important trigger for central

**TABLE 4** Quantitative Sensory Testing results of the ankle joints in patients with haemophilia (PwH) and healthy controls (Con)

| Parameter          | Group | T0              | T1              | ANOVA | PwH vs Con |
|--------------------|-------|-----------------|-----------------|-------|------------|
| CDT (°C)           | PwH   | -4.0 ± 5.4      | -4.6 ± 3.7      | .594  | .778       |
|                   | Con    | -3.2 ± 2.0      | -5.1 ± 5.2      |       |            |
| WDT (°C)           | PwH   | 8.2 ± 3.7       | 9.7 ± 3.8       | .530  | .100       |
|                   | Con    | 7.8 ± 3.1       | 8.4 ± 3.5       |       |            |
| TSL (°C)           | PwH   | 14.6 ± 6.4      | 16.2 ± 4.7      | .475  | .058       |
|                   | Con    | 10.9 ± 6.0      | 15.4 ± 5.3      |       |            |
| CPT (°C)           | PwH   | 8.5 ± 10.9      | 10.3 ± 11.4     | .299  | .860       |
|                   | Con    | 11.9 ± 10.8     | 8.4 ± 9.6       |       |            |
| HPT (°C)           | PwH   | 47.4 ± 2.0      | 47.9 ± 2.0      | .952  | .507       |
|                   | Con    | 46.7 ± 2.5      | 47.5 ± 2.9      |       |            |
| MPS (mN)           | PwH   | 14.0 ± 11.6     | 12.5 ± 19.8     | .000  | .086       |
|                   | Con    | 6.5 ± 5.8       | 6.6 ± 5.9       |       |            |
| MDT (mN)           | PwH   | 13.9 ± 9.8      | 19.4 ± 12.4     | .005  | .213       |
|                   | Con    | 12.0 ± 8.2      | 13.7 ± 11.1     |       |            |
| MPT (NRS)          | PwH   | 28.7 ± 27.5     | 21.9 ± 21.1     | .000  | .000       |
|                   | Con    | 63.5 ± 49.5     | 42.9 ± 24.1     |       |            |
| WUR (NRS)          | PwH   | 2.4 ± 1.4       | 3.7 ± 2.9       | .199  | .046       |
|                   | Con    | 1.8 ± 2.8       | 2.8 ± 2.1       |       |            |
| VDT (x/8)          | PwH   | 5.7 ± 2.3       | 6.3 ± 1.8       | .367  | .923       |
|                   | Con    | 6.3 ± 1.8       | 6.7 ± 1.0       |       |            |
| PPT (N)            | PwH   | 47.2 ± 21.6     | 46.2 ± 25.3     | .636  | .000       |
|                   | Con    | 57.8 ± 21.4     | 60.8 ± 20.8     |       |            |

Results based on n = 61 ankle joints (PwH n = 31, controls n = 30).

CDT, cold detection threshold; WDT, warmth detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold.

**TABLE 5** Quantitative Sensory Testing results of the dominant hand in patients with haemophilia (PwH) (n = 24) and healthy controls (Con) (n = 21)

| Parameter          | Group | T0       | T1       | ANOVA | PwH vs Con |
|--------------------|-------|----------|----------|-------|------------|
| CDT (°C)           | PwH   | -1.5 ± .6 | -1.5 ± .5 | .368  | .942       |
|                   | Con    | -1.6 ± .7 | -1.4 ± .7 |       |            |
| WDT (°C)           | PwH   | 1.9 ± .6  | 2.4 ± .4  | .211  | .922       |
|                   | Con    | 2.1 ± 1.4 | 2.4 ± 1.6 |       |            |
| TSL (°C)           | PwH   | 4.1 ± 2.0 | 4.6 ± 2.2 | .368  | .233       |
|                   | Con    | 3.5 ± 1.5 | 4.6 ± 3.3 |       |            |
| CPT (°C)           | PwH   | 11.8 ± 9.3 | 12.2 ± 8.2 | .190  | .381       |
|                   | Con    | 8.4 ± 8.6 | 12.1 ± 8.1 |       |            |
| HPT (°C)           | PwH   | 43.9 ± 4.7 | 43.8 ± 4.1 | .458  | .219       |
|                   | Con    | 45.4 ± 4.7 | 44.5 ± 3.8 |       |            |
| MPS (mN)           | PwH   | 9.9 ± 8.5  | 8.4 ± 11.0 | .001  | .413       |
|                   | Con    | 6.4 ± 5.7  | 6.5 ± 5.3  |       |            |
| MDT (mN)           | PwH   | 1.7 ± 1.2  | 3.8 ± 7.7  | .000  | .000       |
|                   | Con    | 1.9 ± 1.3  | 2.6 ± 5.1  |       |            |
| MPT (NRS)          | PwH   | 67.3 ± 91.4 | 73.8 ± 83.6 | .000  | .000       |
|                   | Con    | 111.7 ± 88.8 | 104.1 ± 74.3 |       |            |
| WUR (NRS)          | PwH   | 2.6 ± 2.5  | 3.0 ± 2.5  | .717  | .837       |
|                   | Con    | 2.1 ± 1.6  | 3.0 ± 1.8  |       |            |
| VDT (x/8)          | PwH   | 7.5 ± .8   | 7.8 ± .5   | .196  | .672       |
|                   | Con    | 7.7 ± .7   | 7.6 ± .9   |       |            |
| PPT (N)            | PwH   | 43.6 ± 15.3 | 44.8 ± 15.8 | .442  | .023       |
|                   | Con    | 64.0 ± 27.7 | 56.8 ± 19.1 |       |            |

Abbreviations: CDT, cold detection threshold; WDT, warmth detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold.
Based on data from animal models, it is suggested that patients with osteoarthritis and central sensitisation could benefit from desensitising drugs such as pregabalin.11 Especially in the case of PwH, liver and kidney function have to be taken into account. Nevertheless, if there is evidence of such a benefit, this option should be evaluated for PwH.

As shown in Figures 3 and 4, the changes in the pain profiles over the year are almost identical for PwH and controls. Thus, a concurrent increase in pain sensitivity for pressure pain and mechanical pain stimuli and a decrease in the perception threshold for mechanical non-painful stimuli can be observed in both groups. A possible explanation for this could be that pain processing system generally changed over the course of the year. El Tumi and colleagues were able to show that in healthy people, sensitivity to pressure pain, but not heat pain, increases with age.16 Therefore, the changes in the somatosensory profile in PwH, regardless of any bleeding episodes, may be explained by the natural aging process.

Due to the statistically significant differences of QST results between PwH and controls at baseline, there is a need for urgent action. In addition to the treatment of existing pain,17 the primary goal of early tailored (pain) management should also be to prevent pathophysiological changes at peripheral and central levels.3,13 For this purpose, it is not only important to identify the respective pain conditions as early as possible, but also to evaluate the success of the haematological therapy.

Since the severity of haemophilic arthropathy corresponds to an increased sensitivity to pain,6 it must be assumed that the pain profile would have to undergo major changes if the bleeding frequency were to be correspondingly high. Since bleeding events were not considered in this first analysis, this should be further analysed subsequently.

The fact that the development of the QST parameters does not differ substantially between the cohorts could also be due to the fact that all the patients examined with severe haemophilia used prophylactic substitution. Therefore, it would be beneficial to investigate how the pain sensation in PwH develops in countries where no prophylactic therapy is available.

New treatment options, which have been shown to reduce the frequency of bleeding and to improve the joint status in PwH,18,19 should also be evaluated for their effect on pain development– for example, how extended half-life products or corresponding mimetics affect an existing pain condition or whether a delay in the development of chronic pain can be achieved. Lambing et al. showed that chronic pain begins at an average age of 11.5 years in PwH.20 If chronic pain could be further deferred or, in the best case, even avoided, this would contribute significantly to an improved quality of life for the patients affected. To enable this, regular pain assessments using QST or pain

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**FIGURE 2**  Z-transformed Quantitative Sensory Testing profile of patients with haemophilia (PwH) ($n = 24$) and healthy controls (Con) ($n = 21$) at baseline. CDT, cold detection threshold; WDT, warmth detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold. x-axis = mean values of the control group. Results based on $n = 61$ ankle joints (PwH $n = 31$, controls $n = 30$), and $n = 21$ knee joints (PwH $n = 10$, controls $n = 11$).
**FIGURE 3** Z-transformed Quantitative Sensory Testing profile of patients with haemophilia (PwH) \( (n = 24) \) in the 1-year course. CDT, cold detection threshold; WDT, warmth detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold. x-axis = mean values of baseline assessments of PwH. Results based on \( n = 31 \) ankle joints \( n = 10 \) knee joints.

**FIGURE 4** Z-transformed Quantitative Sensory Testing profile of healthy controls \( (n = 21) \) in the 1-year course. CDT, cold detection threshold; WDT, warmth detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold. x-axis = mean values of baseline assessments of controls. Results based on \( n = 30 \) ankle joints, and \( n = 11 \) knee joints.
thresholds could identify changes in the pain processing system at an early stage and enable a targeted approach to the different types of pain (peripheral vs. central).

5 | CONCLUSION

Haemophilic arthropathy at knee and ankle joints leads to various changes in the somatosensory system, affecting peripheral and central levels of the pain processing system. The QST profile between PwH and controls does not seem to deteriorate further over the course of a year under a prophylactic treatment regimen and may only be affected by age-related changes. For the treatment of pain, further knowledge is necessary regarding, for example, the influence of different anti-haemophilic treatment regimens or products on pain in PwH.

6 | LIMITATIONS

A possible reason for the small changes in the QST profile of PwH could be the short observation period of 1 year. One could assume that a longer period may have led to larger pain-specific changes. Additionally, QST may not be sensitive enough to detect very small changes in the somatosensory profile; measurements of pain by QST with even finer distinction and a higher sensitivity could be meaningful for future research. In the absence of known expected effects, it should also be noted that no case number calculation was performed. Likewise, when considering the results of knee joints, the comparatively low number of included cases should be taken into account. The data collected would also be important to analyse in the context of substitution and bleeding episodes, which will be examined in the following analyses. Also, it could be speculated that a current higher pain intensity in PwH could have led to more pronounced results. Also, it can be speculated that there may be an overlap of HIV-induced neuropathy and haemorrhage-related alteration of the somatosensory system in some cases studied. Because the contralateral side, which was affected to different degrees in the individual patients, was also examined in addition to the most painful joint, possible overlaps may also have influenced the results.

ACKNOWLEDGEMENTS

All authors contributed to the research design, analysis, and interpretation of the data as well as the drafting and revision of the manuscript. All assessments were performed by S. Krüger. This study was supported by an investigator-initiated grant provided by Baxalta US Inc., Bannockburn, IL (grant # H16-34965), a member of the Takeda group of companies. The authors would like to thank Shire/Takeda for funding this study.

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

T. Hilberg has received research support and presentation fees from Shire/Takeda but has no interests, which might be perceived as posing a conflict of interest or bias with regard to this study. S. Krüger and M. Herzig has received honoraria and travel support from Shire/Takeda and Swedish Orphan Biovitrum. S. Krüger was an employee at the Department of Sports Medicine at the time of the study and when the manuscript was written but is now employed by Takeda.

DATA AVAILABILITY STATEMENT

The data are not available due to privacy or ethical restrictions.

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