Original Article

Muskuloskeletal

Most subjectively affected joints in patients with haemophilia – what has changed after 20 years in Germany?

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Abstract

Background: In patients with haemophilia (PwH), most frequently affected joints are the ankle, knee and elbow. Due to improved factor therapy in the last decades, these previous findings have to be verified in Germany.

Aim: The aim of this study is to detect the most affected joint, evaluate the significance of the source of pain and determine the point prevalence of back pain in Germany today.

Patients and methods: In a retrospective study, data of n = 300 patients with severe moderate and mild haemophilia were evaluated regarding the most affected joint, the most common source of pain, and the point prevalence of back pain. An anamnesis questionnaire and the German Pain Questionnaire were used for this assessment.

Results: The most affected joint in German PwH is still the ankle (41%), followed by the knee (27%) and the elbow (11%). The most common source of pain is also the ankle joint (32%). Back pain was also identified as one of the most common sources of pain, which is comparable to the elbow (elbow:15%; back:13%). The point prevalence in PwH for back pain was significantly higher compared to the general German population (P = .031).

Conclusion: Our data showed that the ankle is still the most affected joint and the most common source of pain in Germany. These results also showed the relevance of back pain as a pain source. The evaluations also demonstrated the high point prevalence of back pain in PwH. Future therapies should also focus on the spine because joint changes affect posture.

Keywords
back pain, bleeding, haemarthrosis, pain sensation, target joint
1 | INTRODUCTION

The rare disease haemophilia is a blood coagulation disorder with a global prevalence of 20.9 cases per 100,000 males for all severities and types.\(^1\) It is caused by a lack of coagulation factor VIII (Haemophilia A) or IX (Haemophilia B). Patients with haemophilia (PwH) can be affected by different severities based on factor activity (FVIII or IX: severe < 1%; moderate = 1–5%; mild = 5–40%).\(^2,3\) Haemophilia is characterized by recurrent bleedings predominantly in joints and soft tissue. Repeated haemarthrosis result in inflammatory processes in the joints leading to chronic synovitis and encouraging degenerative changes, resulting in haemophilic arthropathy.\(^4,5\) These joint changes are associated with pain as well as swelling, muscle atrophies, strength loss, and restricted range of motion.\(^6–8\) In 2003, the ankle, knee, elbow, hip and shoulder were the most affected joints, accounting for 80% of joint bleedings.\(^9\) The rest of the bleedings occur in other joints or soft tissues. Overall, bleeding negatively impacts quality of life due to chronic synovitis resulting in joint pain, decreased or inhibited motion, and less overall mobility.\(^7,10,11\)

Although the back is not affected by haemophilic arthropathy, Seuser et al. observed in 2008 that 40% of PwH (20 of 49 investigated PwH) reported greater limitations from back pain than from haemophilic arthropathy in daily life.\(^12\) In a further study, PwH showed decreased coordination compared to healthy individuals, which may indicate decreased trunk musculature to compensate lower limbs imbalances.\(^13\) In addition, back pain was identified with questionnaires as the 3rd most common source of pain in German patients with severe haemophilia (n = 71), emphasizing the high incidence and the importance of investigating back pain.\(^14\)

Research indicates that certain joints are affected to different degrees depending on the country the PwH lives in: Wallny et al. identified the ankle joint as the most affected joint in Germany in 2001.\(^14\) In contrast, based on annual bleeding rates, the knee joint was identified as the most frequently affected joint in China.\(^15\) This shows that the most affected joint differs in different global regions and depending on the examination method. Different factor substitution (on-demand or prophylactic) rates might explain these regional differences. In Germany, patients with prophylactic substitution over a mean period of 10 years indicated that the ankle joint was the first to suffer from arthropathies compared to the knee and elbow joints.\(^16\) Over the years, substitution behaviour has changed, and the substitution amount of factor VIII/IX has steadily increased in PwH. Under prophylaxis, the ankle joint becomes more and more affected. Although prophylactic substitution prevents major joint restrictions due to haemorrhages in PwH, many regions have little or no access to factor-replacement treatment.\(^17,18\) Given the ongoing development of factor therapy, it is unclear how the joint situation has changed in Germany over the last 20 years. A particular achievement was improved drug therapy through recombinant and extended-half-life coagulation factors, which are used more frequently today.\(^19\)

Thus, this study aims to update previous data to the main impaired joint and to evaluate whether the ankle joint is still the most frequently affected joint in Germany. The most affected joint is defined as the joint that impairs patients the most in their daily lives. Given the fact that joint restrictions lead to pain and decreased daily activity in PwH, the location of pain should be identified to ensure better clinical diagnostics.\(^20\) Furthermore, this study aims to provide insights into the prevalence of back pain in PwH, as back pain is considered as a more restricting factor than, for instance, pain deriving from target joints in 40% of PwH.\(^12\) The following questions should be answered:

- Is the ankle joint still the most affected joint in German PwH after 20 years?
- Is there a higher point prevalence for back pain in PwH compared to the general German population?

2 | METHODS

2.1 | Subjects

In total n = 300 PwH (n = 217 severe, n = 47 moderate and n = 36 mild) were retrospectively included in this study. Data from five of our prospective studies were collected between 2018 and 2021. The patients were recruited within the Haemophilia and Exercise Project (http://www.haemophilia-exercise.de) as well as in the consulting hours of the German haemophilia centres in Bonn and Münster. PwH A or B between 13 and 84 years were included in the study (Table 1). Exclusion criteria were previous spine and joint surgeries within the previous 6 months, bleeding events in the last 2 weeks, and suffering from other bleeding diseases. Self-administered questionnaires were filled out by the patients for general and pain anamnesis. The questionnaires determined the most affected joint, the current pain status, pain duration, current back pain, factor substitution and medication. For evaluating the current pain status, the ‘German Pain Questionnaire’ was used.\(^21\)

2.2 | Parameters

The standardized questionnaires were used to detect the following endpoints: Most affected joint, most frequent source of pain, point prevalence and pain duration. The most affected joint was detected with the question: ‘Which joint causes the most problems in your everyday life?’ This includes all joint changes in contrast to the most frequent source parameter, which only considers the sensation of pain.

PwH often experience pain due to haemorrhages and have an altered perception of pain; therefore, the most painful joint should be precisely identified.\(^22\) The evaluation of the most frequent source of pain was determined with the question: ‘In which regions of your body does your pain occur?’ This question includes both joints and nonspecific haemophilia body areas such as the back. In this case, only the perception of pain was...
TABLE 1 Demographic data of patients with haemophilia with different severities

| Variables/Severities | Severe (n = 217) | Moderate (n = 47) | Mild (n = 36) | Total (n = 300) |
|----------------------|------------------|------------------|--------------|----------------|
| Age (years)          | 41.6 ± 15.0 (13–84) | 46.4 ± 15.5 (16–76) | 46.3 ± 18.3 (19–79) | 42.8 ± 15.6 (13–84) |
| Weight (kg)          | 83.3 ± 17.3 (50.0–170.0) | 86.7 ± 16.9 (55.0–135.0) | 88.5 ± 15.6 (57.0–145.0) | 84.5 ± 17.1 (50.0–170.0) |
| Height (m)           | 1.80 ± .08 (1.60–2.00) | 1.83 ± .08 (1.70–2.00) | 1.80 ± .06 (1.57–1.90) | 1.80 ± .08 (1.57–2.00) |
| Body mass index (BMI)| 25.7 ± 4.8 (17.0–49.7) | 25.9 ± 5.0 (15.6–40.8) | 27.2 ± 5.1 (17.2–40.6) | 25.9 ± 4.8 (15.6–49.7) |
| Type of haemophilia  | A: 190 A: 27 | A: 38 B: 9 | A: 32 B: 4 | A: 260 B: 40 |
| Factor treatment     | Prophylaxis: 198 On demand: 19 | Prophylaxis: 18 On demand: 29 | Prophylaxis: 1 On demand: 35 | Prophylaxis: 217 On demand: 83 |
| Currently back pain  | No: 90 Yes: 64 Missing data: 63 | No: 21 Yes: 15 Missing data: 11 | No: 16 Yes: 18 Missing data: 2 | No: 127 Yes: 97 Missing data: 76 |

Data presented as mean ± standard deviation (min–max).

Determined. Resulting restrictions in everyday life were not considered with this question. When examining the localization of pain, the duration of pain was also determined in order to differentiate between acute and chronic pain in PwH.

Afterwards, the point prevalence of back pain is precisely identified with the question, ‘Do you have any back pain right now?’ This question was asked separately to evaluate the prevalence of back pain in PwH.

2.3 Statistical analysis

For analysing the joint and pain status of PwH, descriptive statistics were performed using the IBM© Statistical Package for the Social Sciences 27 software (Armonk, NY, USA) for Windows. A binomial test was performed to compare the point prevalence of back pain in PwH with the general population. Based on a point prevalence in the total German population of 37%, an expected probability of .37 was set for back pain in PwH. Using the Chi-squared Test and contingency coefficient, correlations were established between the age groups (four quartiles), pain duration and pain situation. In addition, the severity of haemophilia was also used for the correlation between most affected joint, pain duration and pain situation. A significance level of \( P \leq .05 \) (95% confidence interval) was established for all data.

3 RESULTS

Data of 300 patients regarding their most affected joint and pain situation were included in this study. All patients answered the questionnaires. Seventy-five percent (n = 224) provided information on the prevalence of back pain. Demographic data are shown in Table 1. The average amount of substitution per week in the patients with prophylactic substitution was 6670 IU (median: 6000 IU; min-max: 1000–28,000 IU). N = 143 PwH reported taking medications in addition to factor substitution. Medications were taken in the form of antihypertensive medications (n = 47), nonsteroidal anti-inflammatory drugs or opiates (n = 64) and psychotropic drugs (n = 13).

Regarding the question, ‘which joint causes the most problems in your everyday life?’ data showed that the ankle joint is the most affected joint (n = 41), followed by the knee (n = 27) and elbow (11%; Figure 1 and Table 2). Thirty-six PwH (12%) reported not having any joint problems. The comparison of PwH A with PwH B showed similar proportions for the most affected joint (Table 2). Furthermore, there was no significant \( P > .05 \) correlation between the most affected joint and the severities of haemophilia (Table 3). The ankle is the most frequently affected joint in Germany (Figure 1). In terms of joint-related body side, no differences were observed (right side n = 135; left side
Considering the most frequent source of pain, the ankle joint (31.9%) and the knee joint (20.3%) are the most frequently affected. The third most common source of pain is the elbow (14.6%), followed by back pain (12.7%) (Table 2). In this case, different results are observed in contrast to the question dealing with the most affected joint, in which the back is the fifth most-affected joint. One hundred and forty PwH (47%) reported pain in one area, 72 (24%) in two areas, 29 (10%) in three areas, seven (2%) in four areas, and three (1%) in five areas. Forty-nine (16%) PwH did not report any pain.

PwH reported a point prevalence in back pain of 43.0% \((n = 129)\) (severe = 41.6%; moderate = 41.7%; mild = 52.9%). PwH showed a significantly higher point prevalence for back pain \((P = .031)\). Figure 2 shows the pain duration subdivided in age quartiles. Most PwH \((n = 205 \text{ of } 300; 68\%)\) have pain for at least 6 months. When divided into quartiles, a significant correlation \((\chi^2 = 39.4; P = .002; CC = .341)\) between the age quartiles and the duration of pain can be shown (Figure 2). When considering the severity of haemophilia, there is a significant correlation with the duration of pain \((\chi^2 = 24.0; P = .021; CC = .272)\). The back pain showed no correlation with the severity of haemophilia.

**TABLE 2** Most affected joint and most frequent pain source in patients with haemophilia \((n = 300)\) assessed via questionnaires

| Areas          | All Participants | Subdivision into the type of haemophilia |
|----------------|------------------|-----------------------------------------|
|                | Most affected joint | Most frequent pain source | Areas | Most affected joint in patients with haemophilia A | Most affected joint in patients with haemophilia B |
| Ankle          | 129 (41%) | 146 (32%) | Ankle | 112 (41%) | 17 (41%) |
| Knee           | 86 (27%)  | 93 (20%)  | Knee  | 73 (27%)  | 13 (31%) |
| Elbow          | 35 (11%)  | 67 (15%)  | Elbow | 29 (11%)  | 5 (12%)  |
| Hip            | 13 (4%)   | 15 (3%)   | Hip   | 10 (4%)   | 2 (5%)   |
| Back           | 7 (2%)    | 58 (13%)  | Back  | 6 (2%)    | 1 (2%)   |
| Shoulder       | 6 (2%)    | 21 (5%)   | Shoulder | 5 (2%) | 1 (2%) |
| Other (e.g. Hand) | 1 (0%) | 9 (2%) | Other (e.g. Hand) | 0 (0%) | 1 (2%) |
| No joint problems/ no pain | 36 (12%) | 49 (11%) | No joint problems | 35 (13%) | 1 (2%) |

Data presented as frequency and relative ratio in %. Due to multiple entries (e.g. bilaterally affected joints) the sum is over 300. Percentages may not total to 100% because of rounding.

**TABLE 3** Differentiation of the most affected joint according to the severity of haemophilia

| Areas/Severities | Severe \((n = 217)\) | Moderate \((n = 47)\) | Mild \((n = 36)\) |
|------------------|-----------------------|-----------------------|------------------|
| Ankle            | 101 (44%)            | 16 (33%)             | 12 (33%)         |
| Knee             | 60 (26%)             | 15 (31%)             | 11 (31%)         |
| Elbow            | 28 (12%)             | 5 (10%)              | 2 (6%)           |
| Hip              | 8 (3%)               | 1 (2%)               | 4 (11%)          |
| Back             | 5 (2%)               | 1 (2%)               | 1 (3%)           |
| Shoulder         | 3 (1%)               | 2 (4%)               | 1 (3%)           |
| Other (e.g. Hand) | 0 (0%)             | 1 (2%)               | 0 (0%)           |
| No joint problems | 24 (10%)          | 7 (15%)              | 5 (14%)          |

Data presented as frequency and relative ratio in %. Due to multiple entries (e.g. bilaterally affected joints) the sum is over 300. Percentages may not total to 100% because of rounding.

\(n = 110\). There is a significant correlation between the age quartiles and the most affected joints ankle, knee and elbow \((\chi^2 = 20.2; P = .003; CC = .283)\).
Our data provide an insight into the current joint situation in German PwH. The most affected joint and the most frequent source of pain in PwH is the ankle joint (Figure 1; Table 2). Therefore, in comparison to Wallny et al., there has been no change in the last 20 years with regard to the most frequently affected joint because the ankle is still the most frequently affected joint in Germany. However, the knee joint is affected 13% less frequently today in patients with severe haemophilia (Table 3). The reason could be a reduced number of joint bleedings in the knee and thereby less affected knee joints, but also that ankle joints are more frequently affected compared to the knee joint, both influenced by the prophylactic factor regime as well as local joint stress. Back and elbow are similarly frequently described as the most common source of pain in the present data. In contrast, Wallny et al., 2001 showed a higher prevalence of back pain. One reason for the different results between these two studies could be the higher sample size in the present study (71 vs 300 participants). Nevertheless, the frequency of back pain shows that it has a high relevance in PwH. The present data further indicates that many PwH have pain not only originating from one, but from several joints. Furthermore, a large proportion of PwH showed a pain duration of more than 6 months, which is considered as chronic pain by definition (duration of pain $\geq$ 3 months).

Compared to the general German population, PwH showed a higher point prevalence of back pain (43% vs 37%). Interestingly, patients with mild haemophilia had a higher prevalence of back pain. However, this could be due to the smaller sample size compared to the other groups. Haemorrhages in the joints and muscles in the lower extremities (e.g. ankle joint, knee joint or musculus iliopsoas) can alter posture in the entire musculoskeletal chain. The consequences are extension and flexion deficits and joint instabilities, which affect the gait. The additional reduction in physical activity and the change in muscular load distribution due to bleeding and pain leads to muscular imbalances and a decreased range of motion in the joint. The mentioned factors and the coordinative deficits of PwH can cause back pain due to compensation patterns and are associated with higher loads on the spine.

Concerning the most frequently affected joint, data from the Netherlands and Spain show similar results compared to those from Germany (Table 4). Table 4 shows that the ankle joint is most frequently affected especially in countries where prophylactic substitution dominates. Compared to the ankle joint, the knee joint is particularly muscle-guided. Under prophylaxis conditions, these muscles are strengthened and stabilize the knee joint, thus preventing bleeds. In countries like India or Romania, where prophylactic substitution is limited, knees and elbows are more frequently affected. In both children and adults, the ankle, knee and elbow joints are the most frequently affected by restrictions across all countries. Although there are standard definitions for prophylaxis, the studies do not use them consistently (Table 4). A comparison of the countries in Table 4 shows that only the two countries, Germany and Netherlands, predominantly use prophylactic therapy. Overall, access to prophylactic therapy, which leads to a better joint situation compared to on-demand therapy, is not available in all countries.

It should be noted that different tools were used to determine the most frequently affected joint. As shown in Table 4, the most common diagnostic tool is the clinical joint examination, the bleeding rate and questionnaires about the joint situation. In this study, questionnaires were used which can only evaluate the subjectively reported joint situation. The joint status can be objectively determined when assessing the joint situation through orthopaedic examination, but the influence on the quality of life remains unclear. In contrast to the joint examination, the bleeding rate can be used to determine the target joints. Even if bleeding is associated with pain and limitation of movement, this does not identify the degree of impairment. Hence, the countries are only comparable to a limited extent.

Yet, all studies conducted in different countries revealed the ankle, knee, and elbow joints as the most frequently affected joints. Nowadays, individualized prophylaxis therapy, i.e. substitution depending on body-weight and frequency of bleeding, is recommended. The possibility of prophylactic treatment is only available to a small proportion of patients: 75% of people with bleeding disorders do not have the possibility of receiving adequate treatment. In countries with limited access to factor VIII or IX, the low-dose prophylaxis seems to achieve better results compared to exclusive on-demand therapy regarding bleeding and joint situation. A weekly mean substitution of 30 IU/kg in Tunisia showed a significantly reduced bleeding rate in children with haemophilia compared to on-demand therapy. In China, low-dose prophylaxis also improved the joint situation of PwH. Prophylactic substitution nevertheless shows better long-term effects on the joint status than low-dose prophylaxis.

Although differences in most affected joints and pain sources were identified in the age quartiles, no differences were observed between the severity level and the type of haemophilia. The small sample size in mild and moderate PwH may also influence these results. The ankle thus appears to be the most relevant joint in therapy regardless of the type and severity of haemophilia. A previous study already showed the difficulty of differentiating between moderate and mild haemophilia in the context of clinical characterization. One reason could be that the two severities can no longer be differentiated clinically concerning bleeding and joint situation. Therefore, further investigations are necessary concerning the most affected joint and source of pain with regard to the severity levels.

5 | CONCLUSION

The ankle is the most affected joint and the most frequent source of pain in German PwH. Thus, the order of the most affected joints has not changed in the last 20 years. Overall, the ankle, knee and elbow joints remain the most frequently affected joints in Germany as well. The cause of the most affected joint should be investigated in further studies. One reason might be a change in lifestyle, such as more mechanistically stressful activities. Back pain was shown to be the 4th most common source of pain, in contrast to the findings of Wallny et al. PwH
### TABLE 4 Most affected joints in different countries

| Author          | Region                        | Sample size (severity) | Age in years | Most affected joint | Further affected joints | Assessment tools                  | Factor treatment            |
|-----------------|-------------------------------|------------------------|--------------|----------------------|-------------------------|-----------------------------------|-----------------------------|
| Lambert et al., 2018 | Ivory coast                   | n = 81 (moderate; severe) | Median = 12 (1–39) | Knee                 | Elbow, Ankle            | Clinical joint situation (HJHS)   | Prophylactic (3%); on-demand (98%) |
| Poonnoose et al., 2017 | India, Thailand, Egypt, Brazil, Singapore, South Africa, Venezuela, Brazil, Iran, Argentina | n = 255 (severe) | Median = 10 (5–15) | Elbow (35%) | Knee (29%), Ankle (21%), Shoulder (3%), Hip (2%) | X-ray diagnostics (Petterson-Score); Bleeding rate; Clinical joint situation (WFH) | On-demand (100%) |
| Serban et al., 2017 | Romania                       | n = 37 (mild; moderate; severe) | Mean = 14 ± 3.5 (4–24) | Elbow (41%) | Knee (34%), Ankle (25%) | Clinical joint situation (HJHS) | On-demand (100%) |
| Hua et al., 2015 | China (Shanxi)                 | n = 417 (mild; moderate; severe) | Mean = 28.9 (<1–77) | Ankle (31%) | Knee (30%), Elbow (27%), Hip (7%), Shoulder (6%) | Bleeding rate | Prophylactic (4%); on-demand (96%) |
| Payal et al., 2014 | India (Jodhpur)               | n = 56 (mild; moderate; severe) | (4–18) | Knee (39%) | Ankle (30%), Elbow (20%), Hip (7%), Shoulder (3%), Other (1%) | Clinical joint situation (HJHS) | Dominantly no factor treatment |
| Khanum et al., 2013 | Pakistan                      | n = 92 (mild; moderate; severe) | Mean = 14 (1.5–50) | Knee (51%) | Elbow (23%), Ankle (16%), other or none (10%) | Bleeding rate | Mean: one treatment per year (19%); no factor access (81%) |
| Windyga et al., 2006 | Poland                        | n = 92 (severe) | Mean = 26.6 ± 4.3 (20–36) | Knee | Elbow, Ankle | X-ray diagnostics (Petterson-Score); Clinical joint situation (Gilbert Scale) | Short term prophylaxis (<3 months; 26%); On-demand (74%) |
| Van Genderen et al., 2006 | Netherlands                   | n = 78 (severe) | Mean = 40.5 (18–70) | Ankle (43%) | Knee; Elbow | Questionnaires | Prophylactic (89%); on-demand (11%) |
| Wallny et al., 2001 | Germany                       | n = 71 (severe) | Mean = 43.2 (21–63) | Ankle (45%) | Knee (39%); Spine (14%); Elbow (7%); | Questionnaires | Prophylactic (87%); on-demand (13%) |
| Aznar et al., 2000 | Spain                         | n = 70 (moderate; severe) | Mean = 21.6 (16–26) | Ankle (41%) | Elbow (36%); Knee (23%) | Bleeding rate | Partial prophylactic (56%); on-demand (44%) |
| Hmida et al., 2022* | Germany today                 | n = 300 (mild; moderate; severe) | Mean = 42.8 ± 15.6 (13–84) | Ankle (41%) | Knee (27%); Elbow (11%); Hip (4%); No joint problems (12%) | Questionnaires | Prophylactic (72%); on-demand (28%) |

Data presented as mean ± standard deviation (min–max) or median (min–max).

*Represents the data of the publication.

Note: Percentages may not total to 100% because of rounding. Some percentages and information (e.g. the standard deviation) are missing in the original data. Information about most affected joints has been collected from: HJHS, annual bleeding rate, Visual Analogue Scale, anamnesis and pain questionnaires. HJHS, Haemophilia Joint Health Score; WFH, World Federation of Haemophilia Joint score.
showed a higher point prevalence in back pain compared to the German population, suggesting that clinical attention should also be paid to the back in diagnostics and therapy to focus on potential back impairment in the treatment and prevent motion and gait disorders in PwH. This can be implemented, for example through adapted strength training for the back. Furthermore, PwH should be informed more about a proper lifestyle and suitable as well as unsuitable sports. In addition to a haemophilia-specific exercise program, aids such as insoles can be employed to improve the joint status and the quality of life of PwH.

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AUTHOR CONTRIBUTION
JH, TH and AS performed chart review, data collection and wrote the paper. JH, SK, PR, CK and AF performed chart review and collection of clinical data; FT, HR and JO analysed results and edited the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, JH, upon reasonable request.

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