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Assessment of the burden of outpatient clinic and MRI-guided needle muscle biopsies as reported by patients with facioscapulohumeral muscular dystrophy

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ABSTRACT

Muscle biopsies are used in clinical trials to measure target engagement of the investigational product. With many upcoming therapies for patients with facioscapulohumeral dystrophy (FSHD), the frequency of biopsies in FSHD patients is expected to increase. Muscle biopsies were performed either in the outpatient clinic using a Bergström needle (BN-biopsy) or in a Magnetic Resonance Imaging machine (MRI-biopsy). This study assessed the FSHD patients' experience of biopsies using a customized questionnaire. The questionnaire was sent to all FSHD patients who had undergone a needle muscle biopsy for research purposes, inquiring about biopsy characteristics and burden, and willingness to undergo a subsequent biopsy. Forty-nine of 56 invited patients (88%) completed the questionnaire, reporting on 91 biopsies. The median pain score (scale 0-10) during the procedure was 5 [2-8], reducing to 3 [1-5] and 2 [1-3] after one and 24 h, respectively. Twelve biopsies (13.2%) resulted in complications, eleven resolved within 30 days. BN-biopsies were less painful compared to MRI-biopsies (median NRS: 4 [2-6] vs. 7 [3-9], $p = 0.001$). The burden of needle muscle biopsies in a research setting is considerate and should not be underestimated. MRI-biopsies have a higher burden compared to BN-biopsies.

1. Introduction

1.1. Expected increase in biopsy procedures

Facioscapulohumeral Dystrophy (FSHD) is one of the most common inherited myopathies affecting roughly 1:10,000 people [1,2]. Symptoms usually start with weakness of the face, shoulder and upper arm muscles, progressing into weakness of the leg, girdle and trunk muscles [3]. FSHD is diagnosed by genetic testing using blood samples, so most FSHD patients have never undergone a muscle biopsy before participating in a trial. However, phase I and II clinical trials are expected to include muscle biopsies to demonstrate proof of target engagement at a molecular level. FSHD is caused by expression of the transcription factor DUX4 and its downstream genes in muscle cells [4]. Thus, examination of treatment effects in FSHD will mainly comprise of comparing pre- and post-dose gene expression profiles in muscles cells. With the improved understanding of the pathophysiology and the development of innovative therapies, a significant increase in the number of clinical trials, and therefore muscle biopsies, is expected in the near future [5].

1.2. Two biopsy techniques

A muscle biopsy can be performed in the outpatient clinic or in a Magnetic Resonance Imaging (MRI) machine. Muscle biopsies in the outpatient clinic are easier to perform and schedule, but lack the precision of biopsies performed in the MRI which allows targeting of specific areas in the muscle [6,7]. The latter may be beneficial for FSHD, because (1) in some patients muscle atrophy is pronounced and a specific area needs to be targeted to obtain

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sufficient muscle tissue, (2) affected muscles have small patches of disease activity which can be identified as an increased signal intensity using short tau-inversion recovery sequences (STIR+) in the MRI machine [7,8].

1.3. Bergström needle biopsy procedure

An outpatient clinic biopsy using a Bergström needle (BN-biopsy) starts with marking the targeted area on the skin. After injecting local anesthesia, a small incision (ca. 5 mm) is made in the skin through which the BN-needle (5 mm) is inserted [6]. While applying negative pressure, muscle tissue is cut and collected. After gathering enough tissue, the incision is closed with adhesive plasters and a pressure bandage is applied for 24 h.

1.4. MRI guided biopsy procedure

An MRI-guided biopsy (MRI-biopsy) starts with scanning the patient in the MRI-machine [7]. Using these images, the appropriate target area and needle trajectory is determined. The biopsy is then performed while the patient still lies on the MRI table. After injecting local anesthesia, a small incision is made (ca. 5 mm) and an MRI-compatible trocar (3.4 mm) is inserted. A repeat scan is performed to verify the position of the trocar and to adjust the position of the trocar if necessary. A vacuum-assisted needle (3.7 mm) is then used to perform the biopsy. A final scan is made to confirm the biopsy site, followed by closing the incision with adhesive plasters and applying a pressure bandage for 24 h.

1.5. Aim of this study

Based on the different methods, we hypothesized that MRI-biopsies are expected to be more burdensome than BN-biopsies, because of the additional scanning, repositioning of the needle and gathering the muscle tissue using suction instead of cutting. However, little is known about the burden and possible complications of muscle biopsies in FSHD patients or the differences in burden between BN-biopsies and MRI-biopsies. In this retrospective, observational study we aimed to assess the burden of muscle biopsies performed in research setting in FSHD patients.

2. Methods

2.1. Study design

This was an observational, retrospective questionnaire study. Eligible patients were invited by e-mail including a link to the electronic questionnaire. After 1.5 months, a reminder e-mail was sent out. After three months, non-responders were invited by phone. After four months, the questionnaire was closed.

2.2. Study population

All Dutch-speaking adult FSHD patients who underwent needle muscle biopsies for research purposes were invited to participate. Five different studies involving BN- or MRI-biopsies were identified from which the participants received an invitation [9–13]. Four studies were performed in the Radboudumc (Nijmegen, The Netherlands) and one in the Centre for Human Drug Research (CHDR, Leiden, The Netherlands). In summary, the studies aimed to (1) measure the specific force in FSHD muscle tissue (Radboudumc, BN- or MRI-biopsies), (2) describe the inflammatory response in muscle cells (Radboudumc, BN- or MRI-biopsies), (3) explore eligibility of whole-body MRI and muscle biopsies for clinical trials (Radboudumc, BN-biopsies), or (4) test the safety of losmapimod treatment in a phase I (CHDR, BN-Biopsies) and a phase II clinical trial (Radboudumc, BN-biopsies) [9–13]. All FSHD patients participating in these studies had genetical confirmation of FSHD based on the global guidelines [14]

2.3. Questionnaire

A Dutch questionnaire was developed in Castor EDC inquiring about demographic characteristics, muscle biopsy experience and willingness to undergo a subsequent biopsy [15]. The questionnaire was adapted from the questionnaire in a recent study on the burden of muscle biopsies in Duchenne muscular dystrophy [16]. The questionnaire consisted of 5-point Likert scale questions and open questions (e.g. number of days until pain free). An English version of the questionnaire can be found in Appendix A.

Demographic characteristics consisted of date of birth, sex, self-reported disease severity (ranging from 1 – ‘no symptoms’ to 5 – ‘very severe symptoms’) and the number of muscle biopsies that had been performed. Responders were asked to report on the characteristics, physical and emotional burden on subsequent biopsies separately.

Biopsy characteristics consisted of which muscle had been biopsied, for which study it was performed, whether it was a BN- or MRI-biopsy and the date of the procedure. The physical aspects consisted of: pain level on a numeric rating scale (NRS) from 0-10 during biopsy, one hour and 24 h afterwards, number of days until pain free, number of days until full use of the biopsied muscle was possible, the development of complications (yes/no complication followed by multiple answer options of the most common complications: hematoma, numbness of the skin, muscle weakness, infection, other) and duration of complications (number of days), the use of analgesics (yes/no analgesics and which one), and if a scar remained (yes/no scar, size of the scar in mm, 1 – ‘not burdensome’ to 5 – ‘ very burdensome’).

Emotional aspects included fear and reluctance before the biopsy (1 – ‘no fear’ or ‘no reluctance’ to 5 –‘a lot of fear’ or ‘a lot of reluctance’) and the overall experience of the procedure in hindsight (1 – ‘a lot better than expected’ to 5 – ‘a lot worse than expected).

Lastly, responders were asked about their willingness to undergo a subsequent muscle biopsy with answer options ‘willing’, ‘only willing in case of a drug study’, ‘not willing’, ‘do not know’).

2.4. Data analysis

The data was analyzed using IBM SPSS statistics version 27.0 (IBM Corp, Armonk, NY, USA). Figures were created using GraphPad Prism version 9.0.0 for Windows (GraphPad Software, San Diego, California USA). Ordinal outcomes were reported in percentages and continuous outcomes are reported as median [interquartile range] as all continuous data were not distributed normally.

Demographic data was analyzed for all responders and for two subgroups: responders who reported on at least one BN-Biopsy and responders who reported on at least one MRI-biopsy. As some responders reported on multiple biopsies, the number of biopsies is not equal to the number of responders and some responders are in both the BN- and MRI-biopsy group.

Mixed model analyses were used to compare BN- and MRI-biopsies regarding pain scores, days until pain free and full use, and the overall experience in hindsight. Generalized Estimating Equations (GEE) were used to compare BN- and MRI-biopsies regarding the frequency of analgesic use (Binary GEE), the number of responders reporting one or more complications (Binary GEE), and the total number of complications (Poisson distribution GEE). A p-value <0.05 was considered statistically significant. As this

study is of an explorative nature, no correction for multiple testing was applied.

2.5. Ethical consideration

The protocol was approved by the local ethics committee (CMO-nr: 2020-6981). The data was handled according to Good Clinical Practice guidelines and the local privacy laws.

3. Results

3.1. Demographics

Fifty-six patients who underwent at least one muscle biopsy in one of the studies were identified and received the questionnaire, which was completed by 49 (88%) responders. Two (4%) patients refrained from participation indicating they could not remember sufficient details from their biopsy procedure and five (9%) patients did not complete the questionnaire. The 49 responders reported having undergone a total of 99 biopsies, but complete data of 91 biopsies was available. The median age of the responders was 54 years [44.5-58.5] with 29 (59.2%) responders being male (Table 1). Self-reported disease severity was most often reported as moderately affected (40.8%). Thirty-three (67.3%) responders underwent two muscle biopsies, and biopsies were mostly taken from the vastus lateralis (30.8%) or gastrocnemius (24.2%) muscles. The median time passed since the procedure for 47 biopsies (51.6%) was 18 [13-30] months. Fifty-five (60.4%) of the biopsies were BN-biopsies, 31 (34.1%) MRI-biopsies and five biopsies (5.5%) unknown. Five (10.2%) responders reported on at least one BN- and MRI-biopsy.

3.2. Burden of muscle biopsies

The median reported pain score was 5 [2-8] during the biopsy, 3 [1-5] after one hour, and 2 [1-3] after 24 h. Responders reported to be pain free after 3 [1-7] days and could use the biopsied leg fully after 2 [1-5] days (Fig. 1a). When comparing the different muscles, biopsies from tibialis anterior were the least painful with a median pain score during procedure of 3 [2-7] and biopsies from the vastus lateralis were the most painful with a median pain score during the procedure of 6 [3-8] (Fig. 1b). Analgesics had been taken after 27 (29.7%) biopsies, with paracetamol being the most common analgesic taken (19.8%). Twenty-five complications were caused by 12 (13.2%) biopsies, most commonly local hematoma (n = 10, 40%), muscle weakness (n = 5, 20%), and numbness of

Table 1
Responders and biopsy characteristics.

	All Biopsies (N = 91) N (%)	BN-Biopsies (N = 55) N (%)	MRI-Biopsies (N = 31) N (%)
Unique Responders	49	25	20
Male	29 (59.2)	18 (72.0)	9 (55.0)
Female	20 (40.8)	7 (28.0)	11 (45.0)
Age, median [IQR]	54 [45-59]	53 [43-57]	55 [44-58]
Disease severity			
No symptoms	2 (4.1)	1 (4.0)	0 (0.0)
Mild	12 (24.5)	6 (24.0)	6 (30.0)
Moderate	20 (40.8)	12 (48.0)	7 (35.0)
Severe	14 (28.6)	6 (24.0)	6 (30.0)
Very Severe	0 (0.0)	0 (0.0)	1 (5.0)
Number of Biopsies*			
One	9 (18.4)	1 (4.0)	6 (30.0)
Two	33 (67.3)	21 (84.0)	11 (55.0)
Three	4 (8.2)	1 (4.0)	2 (10.0)
Four	3 (6.1)	2 (8.0)	1 (5.0)
Months passed since biopsy, median [IQR]**	18 [13-30] (n = 47)	17 [13-22] (n = 24)	16 [13-24] (n = 19)
Biopsied Muscle			
Vastus lateralis	28 (30.8)	18 (32.7)	10 (32.2)
Vastus medialis	9 (9.9)	6 (10.9)	3 (9.7)
Tibialis anterior	17 (18.7)	12 (21.8)	3 (9.7)
Gastrocnemius	22 (24.2)	11 (20.0)	10 (32.2)
Other	10 (11.0)	5 (9.1)	4 (12.9)
Do not remember	5 (5.5)	3 (5.5)	1 (3.2)
Type of Biopsy			
BN	55 (60.4)		
MRI	31 (34.1)		
Other	5 (5.5)		
Study			
Specific force(9)	9 (6.6)	4 (7.2)	4 (12.9)
Inflammatory response(10)	29 (31.9)	2 (3.6)	25 (80.6)
Eligibility clinical trial(11)	0 (0.0)	0 (0.0)	0 (0.0)
Phase I Losmapimod(12)	21 (23.1)	21 (38.1)	0 (0.0)
Phase II Losmapimod(13)	23 (25.3)	23 (41.8)	0 (0.0)
Do not remember	9 (9.9)	5 (9.1)	2 (6.5)

The data of the responders' characteristics (Sex, Age, Disease Severity, Number of Biopsies) are based on the number of unique responders. The data of the biopsy characteristics (Biopsies Muscle and Type of Biopsy) are based on the number of total biopsies. Five responders are in both the BN-biopsy and MRI-biopsy group as they reported on both.
BN-Biopsy = A muscle biopsy performed in the outpatient clinic with a Bergström Needle. MRI-Biopsy = A muscle biopsy performed in the magnetic resonance imaging machine. IQR = Interquartile range. BN= Bergström Needle. MRI = Magnetic Resonance Imaging.
* Responders underwent a total of 99 biopsies, but not all responders reported on every biopsy. Data of 91 biopsies is available.
** A lot of data was missing regarding time passed since the biopsy procedure. Therefore, the number of biopsies reported on for this specific variable is reported and is different from the total number of biopsies.

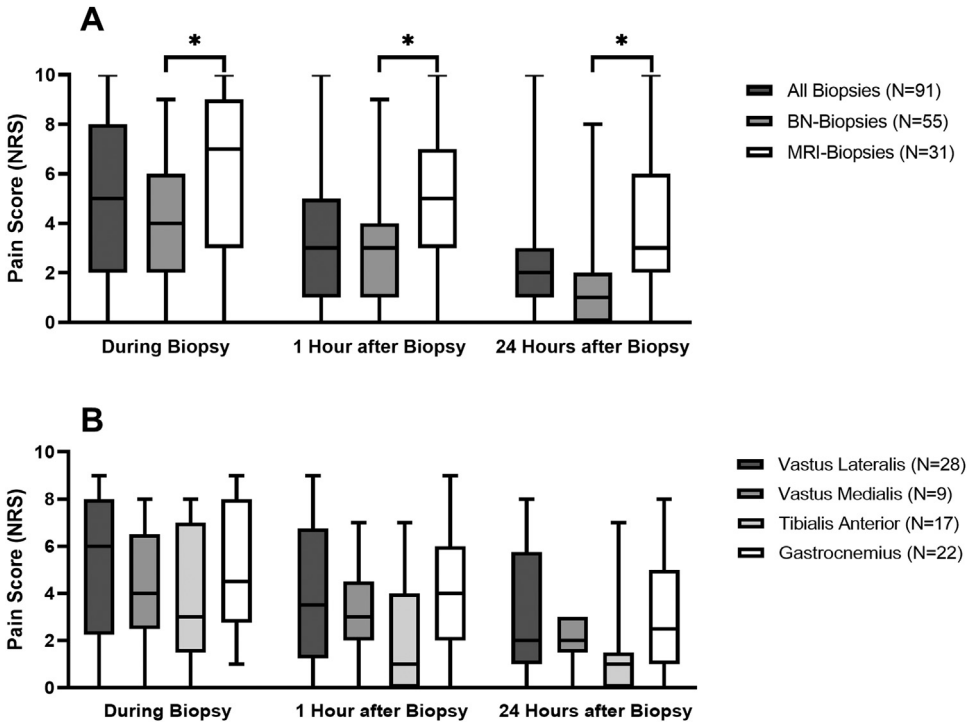

Fig. 1. Pain levels during and after biopsy. Boxplots are shown for the reported pain levels during the biopsy procedure, one hour after the biopsy and 24 h after the biopsy. Each bar represents the median, IQR and total range of the pain scores. The NRS ranged from 0-10.
A. This graph shows the pain scores of all biopsies ($N = 91$) and compares the pain scores of BN-Biopsies ($N = 55$) to MRI-Biopsies ($N = 31$). The data of BN and MR biopsies is not completely independent from each other, as some responders reported on both BN and MR biopsies.
*: Mixed models resulted in a significant difference for all pain scores: $p = 0.003$ during the procedure, $p = 0.000$ after 1 h, and $p = 0.000$ after 24 h.
B. This graph shows the pain scores per biopsied muscle.
NRS= Numeric Rating Scale. IQR= Interquartile range BN-Biopsy = A muscle biopsy performed in the outpatient clinic with a Bergström Needle. MRI-Biopsy = A muscle biopsy performed in the magnetic resonance imaging machine.

the skin at the biopsy site ($n = 4$, 16%) (Fig. 2a). No complications occurred after tibialis anterior biopsies, while two out of nine (22%) biopsies in the vastus medialis and four out of twenty-two (18%) resulted in one or more complications (Fig. 2b). The hematomas resolved in 3 - 21 days; and numbness and muscle weakness in 10-30 days. One responder reported permanent (>999 days) muscle weakness of the biopsied muscle. Thirty-two (35.2%) visible scars were reported, with a median size of 5 [3-5] mm causing no to little burden.

Sixty-eight (74.8%) of the biopsies were preceded by no to little fear, and 61 (67.1%) with no to little reluctance. The overall experience in hindsight was a little to a lot better than expected in 50.6% of the biopsies and a little to a lot worse than expected in 31.9% of the biopsies (Fig. 3).

Twenty-six (53.1%) responders reported to be willing to undergo another muscle biopsy for research, 5 (10.2%) were not willing, 5 (10.2%) were willing only in the case of a drug trial and 13 (26.5%) were unsure (Fig. 4).

3.3. Comparison of biopsy technique

Besides the higher male-female ratio in BN-biopsies, the demographic data of the BN-biopsy and MRI-biopsy groups are comparable (Table 1). BN-biopsies were mostly performed on the vastus lateralis (32.7%), tibialis anterior (21.8%) and gastrocnemius (20.0%), while MRI-biopsies were mostly performed on the gastrocnemius (32.2%) and vastus lateralis (32.2%).

BN-biopsies caused less pain compared to MRI-biopsies: the median pain scores were 4 [2-6] vs. 7 [3-9] ($p = 0.003$) during the procedure, 3 [1-4] vs. 5 [3-7] ($p = 0.000$) after 1 hour, and 1 [0-2] vs. 3 [2-6] ($p = 0.000$) after 24 h (Fig. 1a). Reported recovery of BN-biopsies did not differ from MRI-biopsies: responders were pain free after 3 [1-5] days vs. 5 [4-8] days ($p = 0.937$) and could fully use the biopsied leg after 2 [1-5] days vs. 3 [2-8] days ($p = 0.925$). Sensitivity analysis in which outliers were excluded gave similar results.

Analgesics were used less frequently after BN-biopsies compared to MRI-biopsies (11 (20%) vs. 14 (45.2%), respectively, $p = 0.029$). No difference was found in the number of responders reporting complications (5 (20%) vs. 6 (30%), $p = 0.174$) or the complication rate (11 vs. 11, $p = 0.360$) between BN- and MRI-biopsies.

The analysis showed that the overall experience in hindsight was better in BN-biopsies compared to MRI-biopsies (2 [1-3] vs. 4 [2-5], $p = 0.002$).

4. Discussion

The expected increase in clinical trials in FSHD requiring muscle biopsies calls for a better understanding of the burden of muscle biopsies and the willingness of patients to undergo muscle biopsies. This study showed a relatively high, but short-term burden of biopsies, favoring BN- biopsies compared to MRI-biopsies. Complications were frequent but short-lasting. The tibialis anterior muscle seems to be the most patient-friendly biopsy site.

4.1. Pain score

The pain score and number of complications were higher than expected based on our clinical experience with BN-biopsies. However, our data corresponds well with other studies reporting

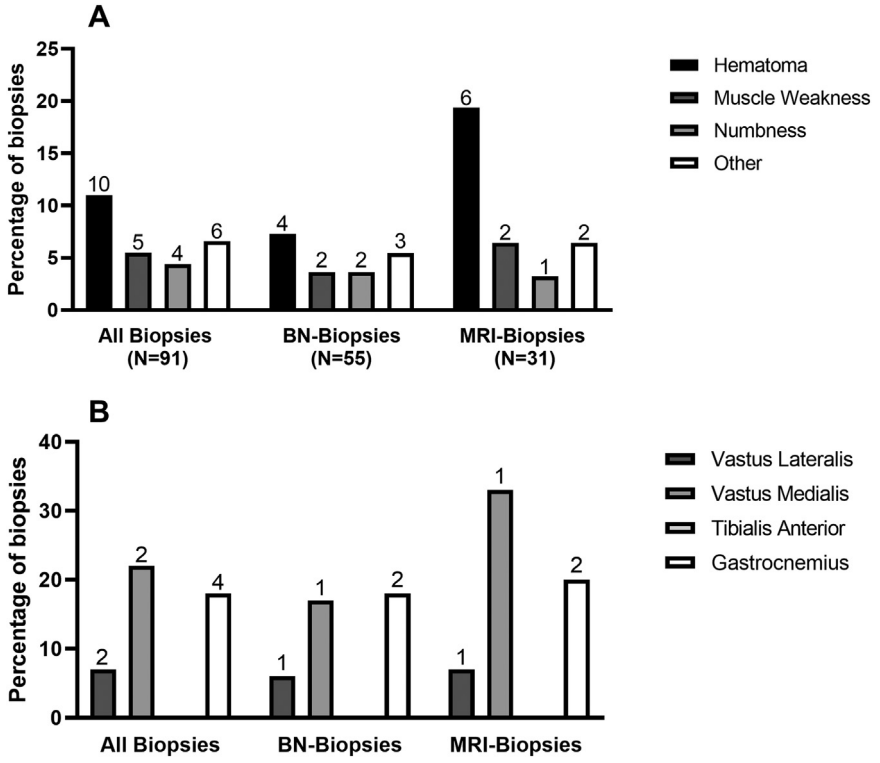

Fig. 2. Complication rate of biopsies.
A. The height of the bars indicate the percentage of the biopsies that resulted in the concerned complication. The numbers above the bars indicate the absolute number of the reported concerned complication. No significant difference was found in the number of responders reporting one or more complications (5 (20%) vs. 6 (30%), $p = 0.174$) or complication rate (11 vs. 11, $p = 0.360$) between BN- and MRI-biopsies.
B. The height of the bar indicate the percentage of biopsies that resulted in one or more complications per biopsied muscle. Noticeably, none of the tibialis anterior biopsies resulted in a complication.
BN-Biopsy = A muscle biopsy performed in the outpatient clinic with a Bergström Needle. MRI-Biopsy = A muscle biopsy performed in the magnetic resonance imaging machine.

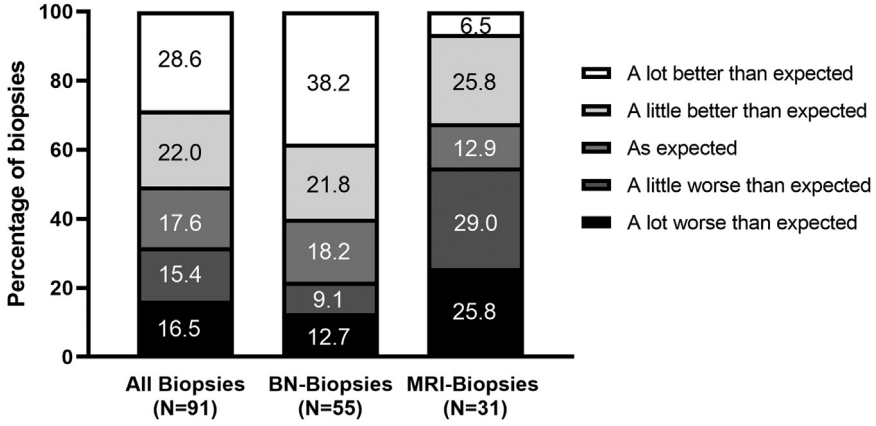

Fig. 3. The experience of the biopsies in hindsight. Responders were asked if the biopsy was better, worse or as they had expected it. Data is based on number of biopsies as shown below each bar. The numbers in the blocks are the percentages for each answer option. The experience of BN-biopsies was considered significantly better compared to MRI-biopsies (estimated means (SD): 2.3 (0.2) vs. 3.5 (0.3), $p = 0.002$).
BN-Biopsy = A muscle biopsy performed in the outpatient clinic with a Bergström Needle. MRI-Biopsy = A muscle biopsy performed in the magnetic resonance imaging machine.

on BN-biopsies. Dengler et al. reported a mean NRS of 4.5 (±2.7) of biopsies in the m. deltoideus from 33 ALS patients [17]. Another study with 17 patients showed a NRS range of 4-6 in m. vastus lateralis biopsies [18]. Unfortunately, these studies did not report on the number of complications, so we cannot verify the complication rate of our study. Possibly important to note is that Dengler et al. stab incised the muscle fascia before entering the muscle with the BN. The BN-biopsies in the included studies in this paper penetrated the muscle fascia with the BN. It is unclear which method is less burdensome and needs to be investigated in future studies.

4.2. Benefits of MRI-biopsies

In line with the more extensive nature of the MRI-biopsy procedure, a higher patient burden was reported compared to BN-biopsies. MRI-biopsies should therefore only be performed if the additional benefits outweigh the burden, which might be the case

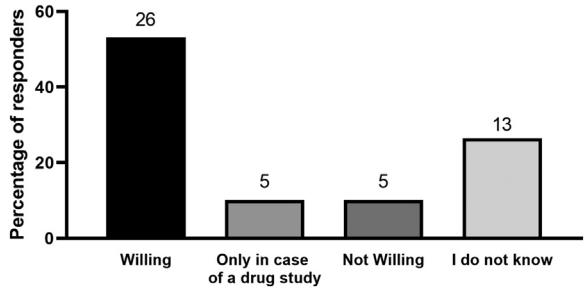

Fig. 4. Willingness to undergo a subsequent biopsy. Percentage of responders (N = 49) indicating if they were willing to undergo a subsequent biopsy for scientific purposes. The numbers above the bars represent the number of responders.

for FSHD [7]. The phase I and II trials investing losmapimod used BN-biopsies to target STIR+ lesions (1-2 cm) previously found on MRI [12,13]. Prior to the biopsy procedures, participants would be scanned with markers on the legs to acquire the coordinates to a STIR+ lesion. Before starting the BN-biopsy procedure, the markers (or a grid with marker placement) would need to be placed in the exact same way on the leg to target the identified STIR+ lesion using the MRI-acquired coordinates. This method involves multiple steps that are error-prone, especially considering the small sizes of the STIR+ lesions. Confirmation of the needle in a STIR+ lesion using an MRI-biopsy would have been more reliable, and MRI-biopsies could therefore be considered the superior method when targeting the aberrant DUX4 expression, even if the burden is higher. Furthermore, it was reported that the tissue size of MRI-biopsies was similar or larger than BN-biopsies and of high enough quality for histological evaluation [7]

4.3. Other biopsy techniques

The biopsies reported on in this study were all performed using Bergström needles or the MRI-compatible equivalent needle. However, different materials and techniques are available which might be more patient friendly. Firstly, in open biopsies an incision of ca. 3-4 cm is made, and muscle samples are cut from the muscle using a scalper or scissor. Open biopsies in the deltoid muscle were reported to be less painful compared to needle biopsies [17]. However, because of the larger incision, a more visibly scar may remain after open biopsies [16]. Secondly, the most similar to the BN-biopsy is a biopsy using a conchotome. After local anesthesia, a 1-2 cm incision is made in the skin and the muscle fascia is penetrated with a scalpel blade. The conchotome is then used to collect muscle tissue [19]. The conchotome may lead to more intramuscular bleeding, but it is easier to target a specific area of the muscle using the conchotome [20]. Thirdly, microbiopsies were not considered painful with NRS ranging from 0 to 1. However, the obtained sample weight is considerably lower (15–55 mg) compared to BN-biopsies (145–218 mg) [18]. Lastly, automatic biopsy devices can be used. Compared to Bergström needles, they require a smaller incision, and the procedure is faster as the devices quickly ejects and retracts the needle. Just as with microbiopsies, the samples are substantially smaller (15 mg) [21]. A recent systematic review compares the aforementioned methods regarding sample yield, diagnostic contributions and complication rate [22]

Currently, the Bergström needle biopsies are most often used in FSHD trials, because they allow for large samples, are cheap and easy to perform, and do not have long-term burden. Careful consideration about the necessary weight of the muscle tissue samples might enable the use of microbiopsy or automatic device biopsy, resulting in a more patient friendly procedure.

4.4. Strengths and limitations

This is the first study directly comparing BN-biopsies and MRI-biopsies. The high response rate on the questionnaire allowed for a reliable comparison between the BN- and MRI-biopsies, although selection bias might be present based on the inclusion criteria of the studies.

All the biopsies were performed in the Netherlands with the majority having been performed in the same hospital using the same BN-biopsy or MRI-biopsy protocol. The study at CHDR used the same BN-biopsy protocol as the Radboudumc BN-biopsy, but slight differences in the procedure cannot be ruled out. Still, we estimate a low chance of confounding of the data due to differences in the procedures.

Furthermore, both the Radboudumc and CHDR site have multiple years of experience in performing BN-biopsies, in total >100 BN-biopsies per year. Muscle MRI-biopsies were performed specifically for the two aforementioned studies. The MRI-biopsies were performed by intervention radiologists who performed >250 MRI-guided biopsies of the prostate or mammae per year, of which the latter used the same biopsy system as the muscle MRI-biopsies. Biased results caused by a possible difference in experience is therefore negligible.

The biggest limitation of this study is its retrospective nature. Most of the biopsies reported on were undergone one to two years before the questionnaire was sent, which may introduce recall bias.

4.5. Future studies

We suggest that upcoming trials will inquire about the burden of the performed biopsies prospectively during trials using our questionnaire with some modifications. We propose adding two questions regarding 12-h and 48-h after biopsy timepoints to gain a more detailed insight on the course of pain levels and complications. Secondly, subsequent biopsies might be experienced differently based on the experience of the previously undergone biopsies. Prospective trials will allow for a reliable analysis on follow-up biopsies. Thirdly, careful documentation on the tissue sample sizes and the quality of the samples would help in distinguishing between biopsy methods and which muscle would be preferred. Our results show that the tibialis anterior is the most patient-friendly biopsy site. However, without reliable data on the quantity and quality of the muscle samples taken from the tibialis anterior, we cannot conclude that the tibialis anterior is the most optimal muscle to use for biopsies in clinical trials.

5. Conclusion

In summary, the burden of muscle biopsies should not be underestimated, but is relatively short-lasting. MRI-biopsies have a significantly higher burden compared to BN-biopsies and should be used only when the benefits of MRI-biopsies are essential for reliable measurements. Despite the high burden, most of the adult responders were willing to undergo a subsequent biopsy for research purposes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Conception and design: J Kools, W Aerts, NC Voermans
Method development: J Kools, W Aerts, EH Niks, NC Voermans

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Reviewing draft: All authors

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2023.04.001.

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