

## QUESTION

### Should foot and ankle stretching and strengthening vs. no intervention be used for ambulant people with Friedreich ataxia??

POPULATION:	ambulant people with Friedreich ataxia?
INTERVENTION:	foot and ankle stretching and strengthening
COMPARISON:	no intervention
MAIN OUTCOMES:	Independence of ambulation; Balance; Falls; Walking capacity; Quality of life; Lower limb strength;

## ASSESSMENT

### Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>Gait instability is the most frequently reported initial symptom in individuals with FRDA, occurring as the first symptom in 76 - 88% of individuals (Reetz et al, 2015). Mobility typically declines, with loss of mobility for individuals with onset &lt;15 years of age typically 11.5 years after first symptom onset; 18.3 years for individuals with onset 15-24 years of age and 23.5 years for individuals with onset &gt;24 years (Rumney et al, 2020).</p> <p>There are significant gait pattern changes in people with FRDA, including increased double stance time, decreased swing phase as a percentage of the gait cycle, decreased speed of walking, greater step width, reduced step length (Croarkin et al, 2009; Serrao et al, 2012; Vasco et al, 2016; Stephenson et al, 2015) and increased variability (Serrao et al, 2012; Gouelle et al, 2013). In two separate studies, changes to kinematic parameters around the ankle suggest altered antagonist and agonist activity of the calf and anterior shin muscles during ambulation (Serrao et al, 2012; Vasco et al, 2016).</p> <p>In a separate study, gastrocnemius and soleus muscle length was were measured by the Modified Tardieu Scale in 31 individuals with FRDA (Milne et al, 2016). 39% of ambulant individuals had muscle length changes indicative of contracture in one or both of their gastrocnemius muscles. A decrease in length of these muscles was associated with reduced FIM locomotion subscales (worsening independence during ambulation and stair climbing).</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of the topic.</p> <p>1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably serious, 5/7 indicated serious, 1/7 indicated didn't know if serious.</p> <p>1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably not urgent, 1/7 indicated probably urgent, 5/7 indicated urgent.</p> <p>1/7 indicated the consequences of the disturbance of strength, balance, mobility and reduction of falls were probably a priority, 6/7 indicated priority. (Aug 2020).</p>

### Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input type="radio"/> Trivial</li> <li><input type="radio"/> Small</li> <li><input checked="" type="radio"/> Moderate</li> <li><input type="radio"/> Large</li> </ul>		<p>Ankle &amp; foot stretching and strengthening may be a beneficial strategy to maximise ambulatory function in individuals with FRDA. However, there is no published data or clinical evidence to conclusively recommend these exercises. Active exercise may</p>

- o Varies
- o Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with foot and ankle stretching and strengthening
Independence of ambulation - not measured	-	-	-	-	-
Balance - not measured	-	-	-	-	-
Falls - not measured	-	-	-	-	-
Walking capacity assessed with: 10-m ambulation speed	0 (1 observational study) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,c</sup>	-	27 people with chronic spastic paresis (n=18 had hemiparesis and n=9 had paraparesis) who were involved in a >=1 year self-stretch program (using the Guided Self-rehabilitation Contract to increase adherence) were retrospectively studied. 6 assessments were performed per year. After 1 year, ambulation speed at 10m had increased by 41% (p<0.001) from 0.81 m/s to 1.15 m/s.	
Quality of life - not measured	-	-	-	-	-
Lower limb strength - not measured	-	-	-	-	-

1. Pradines M., Baude M.,Marciniak C.,et al. Effect on Passive Range of Motion and Functional Correlates After a Long-Term Lower Limb Self-Stretch Program in Patients With Chronic Spastic Paresis. . PM R. ; 2018.

- a. All participants had a diagnosis of hereditary spastic paraparesis (not FRDA).
- b. Small sample size (n=35)

produce greater benefits for ambulant individuals. Therefore, muscle strengthening with a stretching component (including eccentric lengthening) as opposed to passive stretching alone is recommended.

In clinical practice, individuals with FRDA often report “less stiffness”, “more movement” and “less pain” because of completing ankle and leg stretching exercises and are often keen to continue these even if clinical outcomes don’t indicate a change.

c. Control (non-stretched) muscles allocated after assessment with allocation determined by the 'coefficient of shortening'.

## Undesirable Effects

How substantial are the undesirable anticipated effects?

### JUDGEMENT

- Large
- Moderate
- Small
- Trivial
- Varies
- Don't know

### RESEARCH EVIDENCE

Outcomes	No of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with no intervention	Risk difference with foot and ankle stretching and strengthening
Independence of ambulation - not measured	-	-	-	-	-
Balance - not measured	-	-	-	-	-
Falls - not measured	-	-	-	-	-
Walking capacity assessed with: 10-m ambulation speed	0 (1 observational study) <sup>1</sup>	⊕○○○ VERY LOW <sup>a,b,c</sup>	-	27 people with chronic spastic paresis (n=18 had hemiparesis and n=9 had paraparesis) who were involved in a >=1 year self-stretch program (using the Guided Self-rehabilitation Contract to increase adherence) were retrospectively studied. 6 assessments were performed per year. After 1 year, ambulation speed at 10m had increased	

### ADDITIONAL CONSIDERATIONS

					by 41% ( $p<0.001$ ) from 0.81 m/s to 1.15 m/s.
Quality of life - not measured	-	-	-	-	-
Lower limb strength - not measured	-	-	-	-	-

1. Pradines M., Baude M., Marciniak C., et al. Effect on Passive Range of Motion and Functional Correlates After a Long-Term Lower Limb Self-Stretch Program in Patients With Chronic Spastic Paresis. . PM R. ; 2018.

a. All participants had a diagnosis of hereditary spastic paraparesis (not FRDA).

b. Small sample size (n=35)

c. Control (non-stretched) muscles allocated after assessment with allocation determined by the 'coefficient of shortening'.

## Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li><input checked="" type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input type="radio"/> No included studies</li> </ul>	Very low certainty of evidence as per the evidence profile table.	

## Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Important uncertainty or variability		

- Possibly important uncertainty or variability
- Probably no important uncertainty or variability
- No important uncertainty or variability

Outcomes	Importance	Certainty of the evidence (GRADE)
Independence of ambulation - not measured	IMPORTANT <sup>a</sup>	-
Balance - not measured	IMPORTANT <sup>b</sup>	-
Falls - not measured	CRITICAL <sup>c</sup>	-
Walking capacity assessed with: 10-m ambulation speed	IMPORTANT <sup>d</sup>	⊕○○○ VERY LOW <sup>e,f,g</sup>
Quality of life - not measured	CRITICAL <sup>h</sup>	-
Lower limb strength - not measured	IMPORTANT <sup>i</sup>	-

- a. Identified as critical (1/6), important (3/6), low importance (2/6) by people with FA and critical by the expert authors for this topic.
- b. Identified as critical (2/5), important (3/5) by people with FA and important by the expert authors for this topic.
- c. Identified as critical (3/5), important (2/5) by people with FA and important by the expert authors for this topic
- d. Identified as critical (2/6), important (3/6) and low importance (1/6) by people with FA and important by expert authors for this topic
- e. All participants had a diagnosis of hereditary spastic paraparesis (not FRDA).
- f. Small sample size (n=35)
- g. Control (non-stretched) muscles allocated after assessment with allocation determined by the 'coefficient of shortening'.
- h. Identified as critical (3/6), important (3/6) by people with FA and critical by the expert authors for this topic
- i. Identified as critical (1/6) and important (5/6) by people with FA and important by expert authors for this topic

## Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

RESEARCH EVIDENCE

ADDITIONAL CONSIDERATIONS

<ul style="list-style-type: none"> <li>○ Favors the comparison</li> <li>○ Probably favors the comparison</li> <li>○ Does not favor either the intervention or the comparison</li> <li>○ Probably favors the intervention</li> <li>● Favors the intervention</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>		<p>A survey designed to systematically collect expert-based opinions from clinicians involved in developing the recommendations for this topic and providing clinical care for individuals with Friedreich ataxia, was conducted. Clinical experts from Australia, Europe, UK, South America, Canada and the USA were asked to consider the harms/benefits of <b>foot and ankle stretching and strengthening as a management strategy for ambulant individuals</b>.</p> <p>Reflecting on the impact of <b>foot and ankle stretching and strengthening</b> on <u>Independence of ambulation</u>, 100% (2/2) clinical experts reported a benefit (large, moderate or small), 0% (0/2) reported no effect and, 0% (0/2) reported observing a harm (large, moderate or small).</p> <p>Reflecting on the impact on <u>Balance</u>, 50% (1/2) clinical experts reported a benefit, 50% (1/2) reported no effect.</p> <p>Reflecting on the impact on <u>Falls</u>, 100% (2/2) clinical experts reported a benefit.</p> <p>Reflecting on the impact on <u>Walking capacity</u>, 100% (2/2) clinical experts reported a benefit.</p> <p>Reflecting on the impact on <u>Quality of life</u>, 100% (2/2) clinical experts reported a benefit.</p> <p>Reflecting on the impact on <u>Lower Limb Strength</u>, 100% (2/2) clinical experts reported a benefit.</p>
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## Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <li>○ No</li> <li>○ Probably no</li> <li>○ Probably yes</li> <li>● Yes</li> <li>○ Varies</li> <li>○ Don't know</li> </ul>	<p>No published evidence.</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if the intervention was acceptable (weighing up the balance between benefits, harms and costs).</p> <p>4/4 indicated foot and ankle stretching and strengthening was reasonable. (Aug 2020).</p>

## SUMMARY OF JUDGEMENTS

JUDGEMENT

	JUDGEMENT						
<b>PROBLEM</b>	No	Probably no	Probably yes	<b>Yes</b>		Varies	Don't know
<b>DESIRABLE EFFECTS</b>	Trivial	Small	<b>Moderate</b>	Large		Varies	Don't know
<b>UNDESIRABLE EFFECTS</b>	Large	Moderate	Small	<b>Trivial</b>		Varies	Don't know
<b>CERTAINTY OF EVIDENCE</b>	<b>Very low</b>	Low	Moderate	High			No included studies
<b>VALUES</b>	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	<b>No important uncertainty or variability</b>			
<b>BALANCE OF EFFECTS</b>	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	<b>Favors the intervention</b>	Varies	Don't know
<b>ACCEPTABILITY</b>	No	Probably no	Probably yes	<b>Yes</b>		Varies	Don't know

## TYPE OF RECOMMENDATION

Strong recommendation against the intervention <input type="radio"/>	Conditional recommendation against the intervention <input type="radio"/>	Conditional recommendation for either the intervention or the comparison <input type="radio"/>	Conditional recommendation for the intervention <input type="radio"/>	<b>Strong recommendation for the intervention <input checked="" type="radio"/></b>
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## CONCLUSIONS

### Recommendation

We recommend ankle and foot strengthening and stretching in combination over no strengthening or stretching in individuals with Friedreich ataxia who are ambulant.

### Justification

There is no published evidence examining the effects of ankle strengthening and stretching exercises for individuals with FRDA. However, in clinical practice ankle strengthening and stretching exercises are included in exercise or rehabilitation programs with an emphasis on full active range of ankle dorsiflexion and eccentric calf activity to allow the appropriate ankle range of movement during stance phase of gait, adequate push-off and ankle dorsiflexion for foot clearance. This needs to occur alongside postural control exercises and a focus on improving balance during single leg stance.

## Subgroup considerations

For ambulant individuals with FRDA who present with more severe levels of calf spasticity, stretching and strengthening may provide greater benefit. Orthotics or pharmacological management of spasticity should be considered if strengthening and stretching are not able to address the impact of ankle dysfunction on gait pattern, falls frequency or independence.

## Research priorities

Future research should evaluate the impact of ankle stretching and strengthening programs on ambulation for individuals with FRDA. These should be evaluated against general exercise programs as well as more costly or aggressive management strategies such as orthotics or pharmacological spasticity management.

### References

- Croarkin E, Maring J, Pfalzer L, Harris-Love M, Siegel K, DiProspero N. Characterizing gait, locomotor status, and disease severity in children and adolescents with Friedreich ataxia. *J Neurol Phys Ther.* 2009;33(3):144-9.
- Gouelle A, Megrot F, Presedo A, Husson I, Yelnik A, Pennecot GF. The gait variability index: a new way to quantify fluctuation magnitude of spatiotemporal parameters during gait. *Gait Posture.* 2013;38(3):461-5.
- Milne SC, Corben LA, Yiu E, Delatycki MB, Georgiou-Karistianis N. Gastrocnemius and soleus spasticity and muscle length in Friedreich's ataxia. *J Clin Neurosci.* 2016;29:29-34.
- Reetz K, Dogan I, Costa AS, Dafotakis M, Fedosov K, Giunti P, et al. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. *Lancet Neurol.* 2015;14(2):174-82.
- Rummey C, Farmer JM, Lynch DR. Predictors of loss of ambulation in Friedreich's ataxia. *EClinicalMedicine.* 2020;18:100213.
- Serrao M, Pierelli F, Ranavolo A, Draicchio F, Conte C, Don R, et al. Gait pattern in inherited cerebellar ataxias. *Cerebellum.* 2012;11(1):194-211.
- Stephenson J, Zesiewicz T, Gooch C, Wecker L, Sullivan K, Jahan I, et al. Gait and balance in adults with Friedreich's ataxia. *Gait Posture.* 2015;41(2):603-7.
- Vasco G, Gazzellini S, Petrarca M, Lispi ML, Pisano A, Zazza M, et al. Functional and gait assessment in children and adolescents affected by Friedreich's ataxia: A one-year longitudinal study. *PLoS One.* 2016;11(9):e0162463.