

QUESTION

Should Ca²⁺ and Vitamin D (500 mg, 800 IU) vs. no treatment be used for all patients with osteopenia and/or low vitamin D levels with Friedreich ataxia??

POPULATION:	all patients with osteopenia and/or low vitamin D levels with Friedreich ataxia?
INTERVENTION:	Ca ²⁺ and Vitamin D (500 mg, 800 IU)
COMPARISON:	no treatment
MAIN OUTCOMES:	Bone mineral density; Fractures;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Data from the FA Clinical Outcome Measures (FA-COMS) registry found 2.1% (23/1104) people with FRDA reported osteoporosis or osteopenia, while 9.7% (107/1104) reported a fracture. None of these were vertebral/spinal or femoral fractures (Lynch, 2017).</p> <p>We note that self-reported data may underestimate the prevalence of low bone health in FRDA since screening is not widely undertaken.</p> <p>A small pilot cross sectional study (n=28) showed that a majority of individuals with FRDA had low 25-OH vitamin D levels (11 with reduced and 7 with deficient levels). (Eigentler et al, 2014). We expect that a substantial proportion of individuals with FRDA will have low aBMD on screening that would warrant supplementation with calcium and vitamin D if nutritional requirements are not being met.</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of osteoporosis.</p> <p>4/7 indicated that the problem was serious, 1/7 indicated probably serious, 2/7 indicated they didn't know if serious.</p> <p>2/7 indicated that the problem was urgent, 3/7 indicated probably not urgent, 2/7 indicated they didn't know if urgent.</p> <p>2/7 indicated that the problem was a priority, 1/7 indicated probably a priority, 2/7 indicated probably not a priority, 2/7 indicated they didn't know if priority. (Aug 2020)</p>

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input checked="" type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>A search of three databases (CENTRAL, MEDLINE, EMBASE) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 16 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p> <p>However, addressing identified nutritional deficiencies in calcium and vitamin D in individuals with low bone health is considered best practice in both adults (e.g., National Osteoporosis Foundation</p>	<p>Avoiding adverse effects of demonstrated deficiencies in calcium and vitamin D intake in at-risk populations is a component of osteoporosis treatment.</p>

	guidelines; https://www.bonesource.org/clinical-guidelines) and children (Galindo-Zavala et al, 2020)	
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Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know 	<p>A search of three databases (CENTRAL, MEDLINE, EMBASE) identified no randomized, non-randomized controlled, cohort and case studies published from 2014 through to 16 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	<p>While routine supplementation of vitamin D3 (e.g., per Institute of Medicine guidelines) is unlikely to be harmful even without having assessed 25-OHD levels, routine calcium supplementation in the setting of adequate intake could lead to hypercalciuria.</p>

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Very low ● Low ○ Moderate ○ High ○ No included studies 	<p>No published evidence in FRDA.</p> <p>Addressing identified nutritional deficiencies in calcium and vitamin D in individuals where low aBMD for age and sex is identified is considered best practice in both adults (e.g., National Osteoporosis Foundation guidelines; https://www.bonesource.org/clinical-guidelines) and children (Galindo-Zavala et al, 2020).</p>	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS			
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability 	<table border="1" style="width: 100%; text-align: center;"> <tr> <td style="width: 33%;">Outcomes</td> <td style="width: 33%;">Importance</td> <td style="width: 33%;">Certainty of the evidence (GRADE)</td> </tr> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	
Outcomes	Importance	Certainty of the evidence (GRADE)			

	<table border="1"> <tr> <td>Bone mineral density - not measured</td> <td>IMPORTANT^a</td> <td>-</td> </tr> <tr> <td>Fractures - not measured</td> <td>CRITICAL^b</td> <td>-</td> </tr> </table> <p>a. Identified as critical (1/6), important (3/6) and low importance (2/6) by people with FA and important by expert authors on this topic.</p> <p>b. Identified as critical (4/6) and important (2/6) by people with FA and important by expert authors on this topic.</p>	Bone mineral density - not measured	IMPORTANT ^a	-	Fractures - not measured	CRITICAL ^b	-	
Bone mineral density - not measured	IMPORTANT ^a	-						
Fractures - not measured	CRITICAL ^b	-						

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"> <input type="radio"/> Favors the comparison <input checked="" type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>No published evidence.</p> <p>Addressing identified nutritional deficiencies in calcium and vitamin D in individuals with low bone health is considered best practice in both adults (e.g., National Osteoporosis Foundation guidelines; https://www.bonesource.org/clinical-guidelines) and children (Galindo-Zavala et al, 2020), and the prevalence of low bone health is likely high in FRDA. While routine supplementation of vitamin D3 (e.g., per the US Institute of Medicine guidelines) is unlikely to be harmful even without having assessed 25-OHD levels, routine calcium supplementation in the setting of adequate intake could lead to hypercalciuria. Thus, an individualized approach is likely preferred.</p>	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>No published evidence.</p>	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using calcium and vitamin D for people with low bone density and/or low vitamin D levels was acceptable (weighing up the balance between benefits, harms and costs).</p> <p>2/3 indicated the intervention was acceptable, 1/3 indicated probably acceptable (Aug 2020).</p>

SUMMARY OF JUDGEMENTS

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

TYPE OF RECOMMENDATION

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

Recommendation

We conditionally recommend against routine calcium and vitamin D supplementation for individuals with Friedreich ataxia, but vitamin D and calcium supplementation should be considered for those with identified nutritional and/or biochemical deficiencies in calcium and vitamin D intake as these are known risk factors for decreased bone health and may contribute to longer-term fracture risk.

Justification

Addressing identified nutritional deficiencies in calcium and vitamin D in individuals with low bone health is considered best practice in both adults (e.g., National Osteoporosis Foundation guidelines: <https://www.bonesource.org/clinical-guidelines>) and children (Galindo-Zavala et al, 2020). However, there may be risks (e.g., hypercalciuria) with universal supplementation. There are no data to suggest any additional benefit of calcium or vitamin D supplementation for bone health beyond the standard daily recommended intakes (DRIs).

Subgroup considerations

This recommendation of for all individuals with Friedreich ataxia. Nutritional requirements vary by age, sex, and size, and so supplementation should be individualized. Vitamin D levels can also be used to guide treatment.

Research priorities

The clinical relevance of various strategies for calcium and vitamin D supplementation to the trajectory of bone health in FRDA can be the focus investigation.

References

Eigentler A, Nachbauer W, Donnemiller E, Poewe W, Gasser RW, Boesch S. Low bone mineral density in Friedreich ataxia. *Cerebellum*. 2014;13(5):549-57.

Galindo-Zavala R, Bou-Torrent R, Magallares-Lopez B, Mir-Perello C, Palmou-Fontana N, Sevilla-Perez B, et al. Expert panel consensus recommendations for diagnosis and treatment of secondary osteoporosis in children. *Pediatr Rheumatol Online J*. 2020;18(1):20.

Lynch D. FA Clinical Outcome Measures (FA-COMS) Registry (unpublished data): clinicaltrials.gov; 2017 [Available from: <https://clinicaltrials.gov/ct2/show/NCT03090789>