

QUESTION

Should insulin alone vs. metformin and/or novel glucose-lowering therapy (e.g., GLP1RA) and insulin be used for children with stabilised diabetes mellitus with Friedreich ataxia?

POPULATION:	children with stabilised diabetes mellitus with Friedreich ataxia
INTERVENTION:	insulin alone
COMPARISON:	metformin and/or novel glucose-lowering therapy (e.g., GLP1RA) and insulin
MAIN OUTCOMES:	Diabetes control/ complications; Acute care utilization; Disease progression; Health-related quality of life;
BACKGROUND:	

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>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of diabetes mellitus.</p> <p>5/7 indicated that the problem was serious, 1/7 indicated probably serious, 1/7 indicated they didn't know if serious.</p> <p>3/7 indicated that the problem was urgent, 2/7 indicated probably urgent, 1/7 indicated probably not urgent, 1/7 indicated they didn't know if urgent.</p> <p>2/7 indicated that the problem was a priority, 4/7 indicated probably a priority, 1/7 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 type="radio"/> Small <input checked="" 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 15 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</p>	

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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 15 July 2020. No further published evidence meeting the search criteria was identified in the Consensus Clinical Management Guidelines for Friedreich's ataxia, 2014.</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.</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%; border-collapse: collapse;"> <thead> <tr> <th style="width: 50%;">Outcomes</th> <th style="width: 20%;">Importance</th> <th style="width: 30%;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Diabetes control/ complications - not measured</td> <td>IMPORTANT^a</td> <td style="text-align: center;">-</td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	Diabetes control/ complications - not measured	IMPORTANT ^a	-	
Outcomes	Importance	Certainty of the evidence (GRADE)						
Diabetes control/ complications - not measured	IMPORTANT ^a	-						

Acute care utilization - not measured	CRITICAL ^b	-
Disease progression - not measured	IMPORTANT ^c	-
Health-related quality of life - not measured	IMPORTANT ^d	-

- a. Identified as critical (1/6) and important (5/6) by people with FA and important by expert authors on this topic.
- b. Identified as critical (3/6), important (2/6) and low importance (1/6) by people with FA and critical by expert authors on this topic.
- c. Identified as critical (1/6), important (4/6) and low importance (1/6) by people with FA and critical by expert authors on this topic.
- d. Identified as critical (2/6) and important (4/6) by people with FA and important by expert authors on this topic.

Balance of effects

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input checked="" type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know	No published evidence.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<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	No published evidence.	<p>The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using insulin alone for children with diabetes was acceptable (weighing up the balance between benefits, harms and costs).</p> <p>1/3 indicated the intervention was acceptable, 2/3 indicated</p>

		they didn't know if acceptable. (Aug 2020).
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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 ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
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CONCLUSIONS

Recommendation

We suggest using insulin alone rather than insulin and other glucose-lowering therapy as the primary treatment for most children (under 18 years old) with FRDA-related diabetes mellitus.

Justification

Children with FRDA-related DM tend to be more predominantly insulin deficient and therefore require insulin as treatment for DM. Additionally, fewer medications are approved for DM management in pediatrics and therefore less is known about their effects, even in “common” forms of pediatric DM.

Subgroup considerations

This recommendation is for children with Friedreich ataxia with stabilized diabetes mellitus. In children with evidence of insulin resistance or at risk of insulin resistance (elevated fasting insulin at diagnosis of DM, elevated c-peptide while on insulin, elevated BMI, family history of Type 2 DM, acanthosis nigricans on exam), additional anti-diabetic agents such as metformin or GLP-1 receptor agonists can be considered.

Research priorities

Additional research is needed to better understand the pathogenesis of DM in FRDA and if, similar to adults with FRDA-DM, there are components of both decreased insulin secretion and increased insulin resistance.