

QUESTION

Should annual fasting glucose and HbA1c (with follow-up OGTT for impaired fasting glucose, 100-125 mg/dL, and/or pre-DM by HbA1c, 5.7-6.4%) vs. universal OGTT (annual vs q2-3y vs q5y) and annual fasting glucose and HbA1c be used for children and adults with Friedreich ataxia?

POPULATION:	children and adults with Friedreich ataxia
INTERVENTION:	annual fasting glucose and HbA1c (with follow-up OGTT for impaired fasting glucose, 100-125 mg/dL, and/or pre-DM by HbA1c, 5.7-6.4%)
COMPARISON:	universal OGTT (annual vs q2-3y vs q5y) and annual fasting glucose and HbA1c
MAIN OUTCOMES:	Diagnosis of DM; Acute care utilization; Disease progression;
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> <p>There is evidence in other forms of DM that OGTT are more sensitive than HbA1c at diagnosing pre-diabetes.</p> <p>From the American Diabetes Association guidelines (2021): "The concordance between the FPG and 2-h PG tests is imperfect, as is the concordance between A1C and either glucose based test. Compared with FPG and A1C cut points, the 2-h PG value diagnoses more people with prediabetes and diabetes".</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: 40%;">Outcomes</th> <th style="width: 20%;">Importance</th> <th style="width: 40%;">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td>Diagnosis of DM - not measured</td> <td>IMPORTANT^a</td> <td style="text-align: center;">-</td> </tr> </tbody> </table>	Outcomes	Importance	Certainty of the evidence (GRADE)	Diagnosis of DM - not measured	IMPORTANT ^a	-	
Outcomes	Importance	Certainty of the evidence (GRADE)						
Diagnosis of DM - not measured	IMPORTANT ^a	-						

	<table border="1"> <tr> <td data-bbox="508 90 955 175">Acute care utilization - not measured</td> <td data-bbox="955 90 1127 175">CRITICAL^b</td> <td data-bbox="1127 90 1430 175">-</td> </tr> <tr> <td data-bbox="508 175 955 250">Disease progression - not measured</td> <td data-bbox="955 175 1127 250">IMPORTANT^c</td> <td data-bbox="1127 175 1430 250">-</td> </tr> </table>	Acute care utilization - not measured	CRITICAL ^b	-	Disease progression - not measured	IMPORTANT ^c	-	
Acute care utilization - not measured	CRITICAL ^b	-						
Disease progression - not measured	IMPORTANT ^c	-						
<p>a. Identified as critical (2/6), important (3/6) and low importance (1/6) by people with FA and important by expert authors on this topic.</p> <p>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.</p> <p>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.</p>								

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"> ○ 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 	<p>No published evidence.</p> <p>Based on additional considerations survey:</p> <ul style="list-style-type: none"> - Not screening or only screening when symptomatic à Harm - A1c and fasting glucose --> benefit <p>OGTT--> mixed.</p>	<p>A survey designed to systematically collect expert-based opinions from clinicians involved in the development of these guidelines 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 annual Hemoglobin A1c testing as a management strategy for children (under 18y) OR adults (18y+).</p> <p>Reflecting on the impact of annual Hemoglobin A1c testing on diagnosis of DM, 68% (17/25) clinical experts reported a benefit (large, moderate or small), 0% (0/25) reported no effect and, 4% (1/25) reported observing a harm (large, moderate or small). 7 clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact on acute care utilization, 52% (13/25) clinical experts reported a benefit, 16% (4/25) reported no effect and, 4% (1/25) reported observing a harm. 7 expert clinicians could not provide any information on this outcome. Reflecting on the impact on disease progression, 36% (9/25) clinical experts reported a benefit, 28% (7/25) reported no effect and, 4% (1/25) reported observing a harm. 8 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact of Oral glucose tolerance tests annually on diagnosis of DM, 52% (13/25) clinical experts reported a benefit (large, moderate or small), 8% (2/25) reported no effect and, 4% (1/25) reported observing a harm (large, moderate or small). 9 clinicians could not provide any information on this outcome. Reflecting on the impact on acute care utilization, 32%</p>

		<p>(8/25) clinical experts reported a benefit, 28% (7/25) reported no effect and, 4% (1/25) reported observing a harm. 9 expert clinicians could not provide any information on this outcome. Reflecting on the impact on <u>disease progression</u>, 40% (10/25) clinical experts reported a benefit, 20% (5/25) reported no effect and, 4% (1/25) reported observing a harm. 9 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact of Fasting blood glucose tests annually on <u>diagnosis of DM</u>, 64% (16/25) clinical experts reported a benefit (large, moderate or small), 4% (1/25) reported no effect and, 4% (1/25) reported observing a harm (large, moderate or small). 7 clinicians could not provide any information on this outcome. Reflecting on the impact on <u>acute care utilization</u>, 60% (15/25) clinical experts reported a benefit, 8% (2/25) reported no effect and, 4% (1/25) reported observing a harm. 7 expert clinicians could not provide any information on this outcome. Reflecting on the impact on <u>disease progression</u>, 40% (10/25) clinical experts reported a benefit, 24% (6/25) reported no effect and, 4% (1/25) reported observing a harm. 8 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact of only screening if patients are symptomatic on <u>diagnosis of DM</u>, 12% (3/25) clinical experts reported a benefit (large, moderate or small), 0% (0/25) reported no effect and, 60% (15/25) reported observing a harm (large, moderate or small). 7 clinicians could not provide any information on this outcome. Reflecting on the impact on <u>acute care utilization</u>, 8% (2/25) clinical experts reported a benefit, 12% (3/25) reported no effect and, 52% (13/25) reported observing a harm. 7 expert clinicians could not provide any information on this outcome. Reflecting on the impact on <u>disease progression</u>, 4% (1/25) clinical experts reported a benefit, 28% (7/25) reported no effect and, 40% (10/25) reported observing a harm. 7 expert clinicians could not provide any information on this outcome.</p> <p>Reflecting on the impact of not screening for diabetes on <u>diagnosis of DM</u>, 4% (1/25) clinical experts reported a benefit (large, moderate or small), 0% (0/25) reported no effect and, 68% (17/25) reported observing a harm (large, moderate or small). 7 clinicians could not provide any information on this outcome. Reflecting on the impact on <u>acute care utilization</u>, 4% (1/25) clinical experts reported a benefit, 4% (1/25) reported no effect and, 64% (16/25) reported observing a harm. 7 expert clinicians could not provide any information on this outcome. Reflecting on the impact on <u>disease progression</u>, 4% (1/25) clinical experts reported a benefit, 16% (4/25) reported no effect and, 52% (13/25) reported observing a harm. 7 expert clinicians could not provide any information on this outcome.</p>
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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 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 annual fasting glucose and HBA1c levels to detect diabetes for people with FA were acceptable (weighing up the balance between benefits, harms and costs).</p> <p>3/3 indicated the intervention was acceptable. (Aug 2020).</p>

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	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 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 checked="" type="radio"/>
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CONCLUSIONS

Recommendation

We recommend *at least* annual screening for diabetes mellitus with HbA1c and fasting plasma glucose in children and adults with Friedreich ataxia, with consideration of an oral glucose tolerance test if impaired fasting glucose or pre-diabetes (from HbA1c) is identified, over universal screening with OGTT. The decision to pursue intermittent oral glucose tolerance tests should be discussed with patients and families on an individualized basis.

Justification

Since individuals with FRDA are clearly at risk for diabetes and pre-diabetes, annual screening with HbA1c and fasting plasma glucose is critical. Once individuals have symptoms related to hyperglycemia, they are at risk for acute complications and annual screening may help diagnose individuals prior to symptom onset.

Subgroup considerations

This recommendation is for adults and children with Friedreich ataxia. In those with symptoms suggestive of diabetes, such as polyuria, polydipsia, or weight loss, we recommend obtaining HbA1c and random plasma glucose level to screen for diabetes. Individuals with these symptoms who are under 18 years of age and/or present as ill should also be screened acutely for ketosis.

Research priorities

The main research priority is to determine whether HbA1c and fasting glucose alone are sufficient for early diagnosis of DM in FRDA. Additional priorities include determining the relative impact of decreased insulin secretion and increased insulin resistance in FRDA-related DM. Finally, it will be important to determine if intervening on early glucose intolerance found on OGTT can meaningfully improve clinical outcomes.

Reference

American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care*. 2021;44:S15-S33.