QUESTION

Should insulin alone vs. metformin and or novel glucose-lowering therapy (e.g., SGLT2i, GLP1RA, DPPIVi) and insulin be used for adults with higher-risk diabetes mellitus (HbA1c>=8.5%, ketones, or acute hyperglycemia), once stabilised, with Friedreich ataxia?	
POPULATION:	adults with higher-risk diabetes mellitus (HbA1c>=8.5%, ketones, or acute hyperglycemia), once stabilised, with Friedreich ataxia
INTERVENTION:	insulin alone
COMPARISON:	metformin and or novel glucose-lowering therapy (e.g., SGLT2i, GLP1RA, DPPIVi) 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
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of diabetes mellitus. 5/7 indicated that the problem was serious, 1/7 indicated probably serious, 1/7 indicated they didn't know if serious. 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. 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)

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	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.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	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.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	No published evidence.	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ 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)
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
○ 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	No published evidence.	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No published evidence.	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were asked if using insulin alone for adults with more severe diabetes was acceptable (weighing up the balance between benefits, harms and costs). 1/3 indicated the intervention was acceptable, 1/3 indicated varied or sometimes acceptable, 1/3 indicated they didn't know

		if acceptable. (Aug 2020).

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
○	○	●	○	○

CONCLUSIONS

Recommendation

There is insufficient evidence to favor either insulin alone or insulin in combination with metformin or novel glucose lowering therapy (e.g., SGLT2i, GLP1RA, DPPIVi), in adults with Friedreich ataxia and higher risk diabetes mellitus (HbA1c ≥ 8.5%, ketones, or acute hyperglycemia).

Insulin is an appropriate treatment, but possible risks and benefits of other medications are unknown in Friedreich ataxia and treatments must be individualized.

Justification

Insulin is an appropriate management strategy and widely used in individuals with significant hyperglycemia and/or ketosis. Possible risks and benefits of other medications are unknown in FRDA and therefore treatment must be individualized.

Metformin is used widely, and is used in some cases of FRDA-related DM. There is a potential risk of lactic acidosis and inhibition of complex I mitochondrial respiratory chain (McCormick et al, 2017; Cameron et al, 2018). If using metformin, one should consider using the lowest necessary dose, ensuring it is withheld during times of illness to avoid additional risk of lactic acidosis. While there are possible benefits with newer anti-diabetic agents such as SGLT-2 inhibitors and GLP-1 receptor agonists with respect to cardiac disease and heart failure, there is no data specifically in FRDA (Marso et al, 2016; McMurray et al, 2019).

The use of SGLT-2 inhibitors has been associated with euglycemic DKA (Rosenstock et al, 2015). Since patients with FRDA-related DM have decreased insulin secretion, ketone monitoring and close follow-up would be needed if starting an individual with FRDA on this class of medication.

Subgroup considerations

This recommendation is for adults with Friedreich ataxia with higher risk diabetes mellitus (HbA1c ≥ 8.5%, ketones, or acute hyperglycemia).

Research priorities

Research priorities include addressing which anti-diabetic agent should be used initially and evaluating specific benefits and risks related to FRDA-DM.

References

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McCormick A, Farmer J, Perlman S, Delatycki M, Wilmot G, Matthews K, et al. Impact of diabetes in the Friedreich ataxia clinical outcome measures study. Ann Clin Transl Neurol. 2017;4(9):622-31.

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