QUESTION

Should insulin therapy – act rapid (different to other people with hyperglycaemia) vs. same as other people with hyperglycaemia be used for people presenting with hyperglycaemia with Friedreich ataxia?	
POPULATION:	people presenting with hyperglycaemia with Friedreich ataxia
INTERVENTION:	insulin therapy – act rapid (different to other people with hyperglycaemia)
COMPARISON:	same as other people with hyperglycaemia
MAIN OUTCOMES:	Diabetes symptoms ; Hospitalisation;

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Individuals with Friedreich ataxia have an increased risk of developing diabetes. Prevalence has been reported to be between 8 and 32% and is several-fold higher than in age-matched controls. Moreover, diabetes onset is often acute in individuals with FRDA, which may require insulin at diagnosis (Cnop et al, 2013).	The Friedreich's ataxia Clinical Management Guideline Patient and Parent Advisory Panel were interviewed on the consequences, urgency and priority of fever, chest infections and UTIs. 4/6 indicated that the problem was serious, 1/6 indicated probably not serious,1/6 indicated they didn't know if serious. 4/6 indicated that the problem was urgent, 1/6 indicated probably not urgent, 1/6 indicated they didn't know if urgent. 4/6 indicated that the problem was a priority, 1/6 indicated probably a priority, 1/6 indicated they didn't know if a 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		Case study evidence only, no comparison between treatments.

Outcomes	№ of	Certainty of	Relative	Anticipated absolute effects* (95% CI)

	participants (studies) Follow-up	the evidence (GRADE)	effect (95% CI)	Risk with same as other people with hyperglycaemia	Risk difference with insulin therapy – act rapid (different to other people with hyperglycaemia)
Diabetes symptoms assessed with: Diabetic ketoacidosis presentation	2 (2 observational studies)[1,2]	⊕◯◯◯ Very low[a,b,c]	-	A 14-year old boy presented with a progressively increasing disoriented and confused state after 2 days of emesis. There was no history of diarrhea, abdominal pain, convulsions, loss of consciousness, or relevant drug/substance abuse. He was diagnosed with diabetic ketoacidosis and treated with IV fluids, potassium, antibiotics. The diabetes was strictly insulin-dependent and ketosis-prone, with immune markers typical of type 1 diabetes absent. The patient was then noted to have difficulties with walking, standing and slurred speech and was subsequently diagnosed with Friedreich ataxia. (Chakraborty et al 2015) An 8 year old girl with insulin-dependent diabetes mellitus was referred to the Neurology department for gait problems. At 7 years of age she developed polyuria, polydipsia, and acute onset vomiting along with high blood sugars, increased urine and blood ketones, and metabolic acidosis. A diagnosis of diabetic ketoacidosis with underlying diabetes mellitus was made, and she was started on insulin along with dietary and lifestyle modifications. A year later, she complained of gait problems - developed gradual onset progressive imbalance for 3 months, frequent falls, could not climb stairs without support. Diagnosis of Friedreich ataxia was subsequently confirmed. (Garg et al 2017)	
Hospitalisation	1 (1 observational study)[1]	⊕◯◯◯ Very low[a,c]	-	A 14-year old boy presented with a progressively increasing disoriented and confused state after 2 days of emesis. There was no history of diarrhea, abdominal pain, convulsions, loss of	

				consciousness, or relevant drug/substance abuse. He was diagnosed with diabetic ketoacidosis and treated with IV fluids, potassium, antibiotics. The diabetes was strictly insulin-dependent and ketosis-prone, with immune markers typical of type 1 diabetes absent. During the course of hospitalisation, the patient was then noted to have difficulties with walking, standing and slurred speech and was subsequently diagnosed with Friedreich ataxia. He was discharged with a split-mixed insulin regimenof NPH and rapid-acting insulins. (Chakraborty et al 2015)

1. Chakraborty P.P., Ray S.,Bhattacharjee R.,et al. First Presentation of diabetes as diabetic ketoacidosis in a case of Friedreich's ataxia. . Clin. Diabetes. 2015;33(2):84-86. ; 2015.
2. Garg M., Kulkarni S.,Shah K.,Hegde A.. Diabetes mellitus as the presenting feature of Friedreich's ataxia.. J. Neurosci. Rural Pract.; 2017.

a. Medical management involved more than insulin therapy.
b. No studies published except for case studies.
c. Case study/s only.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know		Case study evidence only, no comparison between treatments.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with same as other people with hyperglycaemia	Risk difference with insulin therapy – act rapid (different to other people with hyperglycaemia)

Diabetes symptoms assessed with: Diabetic ketoacidosis presentation	2 (2 observational studies)[1,2]	⊕◯◯◯ Very low[a,b,c]	-	A 14-year old boy presented with a progressively increasing disoriented and confused state after 2 days of emesis. There was no history of diarrhea, abdominal pain, convulsions, loss of consciousness, or relevant drug/substance abuse. He was diagnosed with diabetic ketoacidosis and treated with IV fluids, potassium, antibiotics. The diabetes was strictly insulin-dependent and ketosis-prone, with immune markers typical of type 1 diabetes absent. The patient was then noted to have difficulties with walking, standing and slurred speech and was subsequently diagnosed with Friedreich ataxia. (Chakraborty et al 2015) An 8 year old girl with insulin-dependent diabetes mellitus was referred to the Neurology department for gait problems. At 7 years of age she developed polyuria, polydipsia, and acute onset vomiting along with high blood sugars, increased urine and blood ketones, and metabolic acidosis. A diagnosis of diabetic ketoacidosis with underlying diabetes mellitus was made, and she was started on insulin along with dietary and lifestyle modifications. A year later, she complained of gait problems - developed gradual onset progressive imbalance for 3 months, frequent falls, could not climb stairs without support. Diagnosis of Friedreich ataxia was subsequently confirmed. (Garg et al 2017)
Hospitalisation	1 (1 observational study)[1]	⊕◯◯◯ Very low[a,c]	-	A 14-year old boy presented with a progressively increasing disoriented and confused state after 2 days of emesis. There was no history of diarrhea, abdominal pain, convulsions, loss of consciousness, or relevant drug/substance abuse. He was diagnosed with diabetic ketoacidosis and treated with IV fluids, potassium, antibiotics. The diabetes was strictly insulin-dependent and ketosis-prone, with immune markers typical of type 1 diabetes absent. During

				the course of hospitalisation, the patient was then noted to have difficulties with walking, standing and slurred speech and was subsequently diagnosed with Friedreich ataxia. He was discharged with a split-mixed insulin regimenof NPH and rapid-acting insulins. (Chakraborty et al 2015)

1. Chakraborty P.P., Ray S.,Bhattacharjee R.,et al. First Presentation of diabetes as diabetic ketoacidosis in a case of Friedreich's ataxia. . Clin. Diabetes. 2015;33(2):84-86. ; 2015.
2. Garg M., Kulkarni S.,Shah K.,Hegde A.. Diabetes mellitus as the presenting feature of Friedreich's ataxia.. J. Neurosci. Rural Pract.; 2017.

a. Medical management involved more than insulin therapy.
b. No studies published except for case studies.
c. Case study/s only.

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	Very low certainty of the evidence of effects 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
○ 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 symptoms assessed with: Diabetic ketoacidosis presentation	CRITICAL[a]	⊕◯◯◯ VERY LOW[b,c,d]
Hospitalisation	IMPORTANT[e]	⊕◯◯◯ VERY LOW[b,d]

a. Identified as critical by expert authors on this topic.
b. Medical management involved more than insulin therapy.
c. No studies published except for case studies.
d. Case study/s only.
e. Identified as 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.	

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

We suggest routine diabetes screening using an appropriate test in all individuals with Friedreich ataxia who present to the emergency department, even in the event of a seemingly unrelated complaint. Once hyperglycemia has been determined, management in individuals with Friedreich ataxia should not be fundamentally different to the management of hyperglycemia in individuals without Friedreich ataxia, but with the following consideration: individuals with Friedreich ataxia and diabetic ketoacidosis may need a higher dose of insulin therapy as a result of insulin deficiency and insulin resistance in Friedreich ataxia.

Justification

There is an increased risk of diabetes mellitus in individuals with FRDA (even at lower body mass index) and the possibility of substantial insulin deficiency (including diabetic ketoacidosis) in individuals with FRDA.

Individuals with FRDA are more likely to have decreased insulin secretion and therefore faster progression of diabetes mellitus compared to adults without FRDA with type 2 diabetes mellitus.

Subgroup considerations

This recommendation is for individuals with Friedreich ataxia presenting to the emergency department with hyperglycemia.

Research priorities

Future research should aim to examine the current frequency of presentation and management of acute hyperglycemia in individuals with FRDA.

Reference

Cnop M, Mulder H, Igoillo-Esteve M. Diabetes in Friedreich ataxia. J Neurochem. 2013;126 Suppl 1:94-102.