Clinical Management Guidelines for Friedreich Ataxia

Chapter 10. Endocrine and metabolic issues in Friedreich ataxia

Contents

This chapter of the Clinical Management Guidelines for Friedreich Ataxia and the recommendations and best practice statements contained herein were endorsed by the authors and the Friedreich Ataxia Guidelines Panel in 2022.

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10. Endocrine and metabolic issues in Friedreich ataxia

This chapter describes important endocrine and metabolic issues for individuals with Friedreich ataxia, including diabetes, osteoporosis and assessing nutritional status, and strategies for investigation and management. In making recommendations for screening and management of endocrine and metabolic issues, the authors were tasked with answering the following questions:

For individuals with Friedreich ataxia, what management strategies could be implemented for diabetes mellitus? (see 10.1)

For individuals with Friedreich ataxia, what management strategies could be implemented for osteoporosis? (see 10.2)

For individuals with Friedreich ataxia, what management strategies could be implemented to assess nutritional status? (see 10.3)

10.1 Screening and management of diabetes mellitus in Friedreich ataxia

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10.1.1 Friedreich ataxia and diabetes mellitus

It has been known for nearly a century that individuals with Friedreich ataxia (FRDA) are at risk of developing diabetes (DM) (1, 2). Reported prevalence varies between 5% and 40% (3-6). The variability in estimates can, in part, be explained by the cohort evaluated, as well as the tests and thresholds that were used to diagnose DM. Clinically, FRDA-related DM may be under-recognized using current screening practices. In addition, many individuals with FRDA may not meet diagnostic criteria for DM on initial screening, but do have evidence of abnormal glucose metabolism when evaluated with more sensitive tests. For example, in one study of 41 individuals with FRDA without known DM who underwent oral glucose tolerance testing (OGTT), 12% had DM, and 49% of participants had impaired fasting glucose and/or impaired glucose tolerance (7). Finally, DM has been reported to be a presenting feature of FRDA, though rarely (8).

Consensus diagnostic criteria for any form of DM include hemoglobin A1c (HbA1c) ≥ 6.5% (≥ 48mmol/mol), fasting plasma glucose ≥ 126mg/dL (7.0 mmol/L), two-hour glucose after an OGTT ≥ 200mg/dL (11.1 mmol/l), or a random glucose ≥ 200mg/dL (11.1 mmol/l) in a patient with symptoms of hyperglycemia (9); these criteria are also appropriate for diagnosis of FRDA-related DM.

With respect to risk factors for FRDA-related DM, some studies have found an association between longer GAA trinucleotide expansion size in the *FXN* gene and the odds of developing FRDA-related DM, while others have not (5, 7, 10-12). A recent large study found that individuals with FRDA-related DM were older, had longer GAA repeat lengths, and more severe FRDA (5). Having a point mutation in one allele of the *FXN* gene has been associated with increased risk of FRDA-related DM (3). There is evidence that GAA repeat length is most strongly associated with FRDA-related DM in those with FRDA symptom onset at age 8 to 14 years. Additionally, new data supports a relationship between the risk of FRDA-related DM and cardiac disease in FRDA (unpublished data). Though DM is related to heart failure in the general population (13), it is unknown if there is a relationship between the cardiomyopathy and DM in FRDA that is independent of overall disease severity.

In FRDA, both insulin deficiency and insulin resistance have been implicated in the development of DM. The relative contribution of each of these processes may differ across the lifespan. Typically in

children, FRDA-related DM may present acutely with diabetic ketoacidosis, the hallmark of clinically relevant insulin deficiency (14), and in some cases it can be fatal (15). This insulin-dependent ketosis-prone DM may be caused by non-autoimmune loss of the insulin-producing pancreatic beta cells (16). A few reports have described a decreased number of islets and beta cells in the pancreas in individuals with FRDA (7). Other studies found no difference in glucose-stimulated insulin secretion in individuals with FRDA (17, 18), though diminished arginine-stimulated insulin release has been reported (18). The normal oscillatory insulin secretion pattern has been shown to be preserved in FRDA (19).

In addition to insulin deficiency, studies have pointed to defects in insulin action. Insulin resistance has been demonstrated at the whole body and the cellular level (in blood cells, muscle cells and liver cells) (7, 20-22). Insulin resistance may be present even in individuals with FRDA who are not obese as classified by body mass index, due to increased abdominal adiposity (7). Adults may have a more insidious onset of DM, consistent with slowly evolving insulin resistance and insulin deficiency, and may have initial abnormal glucose tolerance preceding overt DM (7). Most of the studies addressing the pathogenesis of DM in FRDA were conducted before the genetic cause of the disease was elucidated (23) and before important concepts in glucose homeostasis were established (24, 25). One of these crucial concepts is that insulin secretion is tightly regulated by insulin sensitivity (25, 26). Under physiological conditions, pancreatic beta cells increase insulin release as needed to maintain normal glucose tolerance. Thus, to interpret the insulin secretory response of the pancreatic beta cells correctly, it needs to be adjusted for insulin resistance (24, 27, 28). This approach has identified pancreatic beta cell dysfunction as central to the development of diabetes in FRDA (7).

10.1.2 Screening for diabetes mellitus

Screening tests for DM in general include measurements of fasting plasma glucose, random plasma glucose (in the setting of suggestive symptoms), HbA1c, and oral glucose tolerance testing (OGTT). Compared with fasting glucose and HbA1c, the two-hour glucose level from an OGTT will result in more diagnoses of DM in the general population as well as FRDA-related DM, and also more diagnoses of pre-DM (29), a condition characterized by abnormal glucose metabolism that may herald future development of DM (9). In FRDA, impaired glucose tolerance from an OGTT has been detected in individuals with normal fasting glucose (7). While in some other diseases with a higher risk of DM, such as cystic fibrosis, there is a recommendation for annual OGTTs (30), there is currently not enough evidence to recommend this screening strategy in FRDA.

10.1.3 Management of diabetes mellitus

Treatment of autoimmune type 1 DM in individuals without FRDA relies on insulin (type 1 DM is due to near complete insulin deficiency) and for metabolic type 2 DM (caused by relative insulin deficiency in the setting of insulin resistance), insulin, metformin, and other glucose-lowering agents are used. FRDA-related DM has features of insulin deficiency, and in some individuals, particularly adults, also insulin resistance. Therefore, for children with FRDA-related DM and for adults with evidence of decreased insulin secretion (as evidenced by low-c-peptide, presence of ketones, or acute hyperglycemia), we recommend insulin as the primary treatment. For adults with FRDA-related DM with evidence of insulin resistance we suggest individualized application of management guidelines for type 2 DM, with particular consideration of the risks and benefits related to comorbidities of FRDA (31, 32). Newer anti-diabetic agents have not been tested in FRDA and there is significant heterogeneity in FRDA-related DM; therefore, a personalized approach is warranted.

Insulin

Most individuals with FRDA-related DM are currently managed with insulin. Insulin has glucose-lowering effects in individuals with all forms of DM, and is necessary in those with minimal insulin secretion. However, side effects such as hypoglycemia may occur; hence there is interest in considering the potential utility of other agents. Additionally, for individuals with excess weight where weight loss is recommended, insulin may make weight loss more difficult. In individuals with FRDA-related DM who may have decreased dexterity, we recommend using available technologies to aid with insulin administration (e.g., pens and pumps) and blood glucose monitoring (e.g., continuous glucose monitors) (33).

Non-insulin treatments

Possible risks and benefits of non-insulin glucose-lowering agents for individuals with FRDA are described below. It is important to remember that there is currently no evidence for or against their use specifically in FRDA, nor have there been FRDA-specific safety studies for non-insulin therapies. Full review of associated risks should be undertaken prior to use of these medications. Evidence for the described therapies comes from the treatment of other forms of DM and theoretical benefits of associated mechanisms of action.

Metformin is being used in individuals with FRDA-related DM (5, 34). Metformin decreases hepatic glucose output and thereby ameliorates fasting glycemia. Lactic acidosis (35) and inhibition of complex I of the mitochondrial electron transport chain (36) are theoretical risks of metformin in all forms of mitochondrial diabetes, including FRDA-related DM. That said, there is no evidence of concern for metformin-related lactic acidosis in individuals with Maternally Inherited Diabetes and Deafness (MIDD) (37), one sub-type of mitochondrial diabetes with available data, and unlike some other disorders affecting mitochondria, FRDA does not carry a known increased risk of lactic acidosis. Therefore, metformin may be a reasonable choice of medication, though healthcare providers should discuss withholding medication during times of illness and use the lowest effective dose.

Sulfonylureas, which act on the pancreatic beta cell to cause insulin release, carry a risk of hypoglycemia but may be considered in those for whom medication costs is a substantial concern, because they are relatively inexpensive (32).

Thiazolidinediones have also been shown to inhibit complex I of the mitochondrial electron transport chain (38). Thiazolidinediones are PPAR-γ agonists. Caution should be used in the context of heart failure or cardiomyopathy (39), which may pose a particular problem in FRDA. For these reasons, thiazolidinediones should not be a primary treatment for many individuals with FRDA-related DM.

Glucagon-like peptide-1 (GLP-1) agonists, which are incretin analogues, have been shown to improve glucose homeostasis in frataxin-deficient mice (40). Additionally, there are possible cardiac benefits of GLP-1 agonists, though this has not been specifically assessed in FRDA (41). A related class of medication, dipeptidyl-peptidase IV inhibitors (DPP4i) act by increasing incretins such as GLP-1. Importantly, data are mixed with respect to the effects of DPP4i in heart failure (42).

Sodium-glucose cotransport 2 (SGLT-2) inhibitors have been shown to benefit individuals with heart failure unrelated to FRDA, even in those without DM (43). It is unknown if these medications will provide a benefit to in individuals with FRDA. Because individuals with FRDA are at risk for diabetic ketoacidosis related to insulin deficiency (14), and SGLT-2 inhibitors pose a risk of ketosis (44), ketone monitoring, with serum β-hydroxybutyrate is recommended (45). Despite limited data, case reports in other types of mitochondrial DM have recommended consideration of GLP-1 agonists or SLGT-2 inhibitors due to favorable cardiac and renal profiles (46).

Best practice statements

Screening All individuals with Friedreich ataxia should have annual screening for diabetes mellitus and symptoms of hyperglycemia (polyuria, polydipsia, unexplained weight loss) should be reviewed with patients and families.
Management Management of diabetes mellitus in Friedreich ataxia should involve diabetes specialists and take an individualized approach.

Recommendations

Grading for strength of recommendation and level of evidence

For the rating of the **strength** of the recommendation, in addition to evidence from studies in FRDA, evidence from like conditions, clinical experience and expert consensus are taken into account when published evidence is not available.

The **level of evidence** is based on published evidence from studies in FRDA. If there is no published evidence in FRDA, evidence from other like conditions or clinical expertise may have been used to make the recommendation – this is graded as 'very low' or in some cases 'low' level evidence. See the table below for an explanation of the symbols used to grade recommendations.

Strength of recommendation	Symbol	Level of evidence	Symbol
Strong for intervention	↑↑	High	⊕⊕⊕⊕
Conditional for intervention	↑	Moderate	⊕⊕⊕◯
Neither intervention nor comparison	—	Low	⊕⊕◯◯
Conditional against intervention	↓	Very low	⊕◯◯◯
Strong against intervention	↓↓		

Screening

Should annual fasting glucose & HbA1c (with follow-up oral glucose tolerance testing (OGTT) for impaired fasting glucose, 100-125 mg/dL, and/or pre-diabetes by HbA1c, 5.7-6.4%) versus universal OGTT (annual vs q2-3y vs q5y) and annual fasting glucose & HbA1c be used for children (under 18y) OR adults (18y+) with Friedreich ataxia?	**Strength**	**Level of evidence***
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 an oral glucose tolerance test. The decision to pursue intermittent oral glucose tolerance tests should be discussed with patients and families on an individualized basis.	↑↑	⊕⊕◯◯

Justification: Since individuals with Friedreich ataxia are clearly at risk for diabetes mellitus (DM) and pre-DM, annual screening with HbA1c and fasting plasma glucose is critical. Once individuals have symptoms related to hyperglycemia, they are at increased 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 old and/or ill-appearing should also be screened acutely for ketosis.

Treatment for adults with lower-risk diabetes (HbA1c < 8.5%, no ketones, no acute hyperglycemia)

Should insulin alone versus metformin or novel glucose-lowering therapy (e.g., SGLT2i, GLP1RA, DPPIVi) be used for initial therapy for adults (18y+) with "lower-risk" diabetes mellitus (HbA1c <8.5%, no ketones, no acute hyperglycemia) with Friedreich ataxia?	**Strength**	**Level of evidence***
There is insufficient evidence to favor either insulin alone or metformin or novel glucose-lowering therapies (e.g., SGLT2i, GLP1RA, DPPIVi) as initial therapy for adults with lower-risk diabetes mellitus (HbA1c < 8.5%, no ketones, no acute hyperglycemia) with Friedreich ataxia. We suggest an individualized approach with either insulin alone, and/or a glucose-lowering agent, with the choice of medication patient dependent, particularly because of the heterogeneity in Friedreich ataxia-related diabetes mellitus.	—	⊕◯◯◯
Justification: While there is little data in Friedreich ataxia-related diabetes mellitus, we suggest following adult guidelines for type 2 diabetes mellitus, which indicate that first line therapy should depend on comorbidities and patient-centered treatment factors (9, 31, 32, 47, 48). Additionally, metformin is used in some individuals with Friedreich ataxia (5). There are concerns related to metformin (inhibition of complex I and risk of lactic acidosis) but one study did not find increased metformin-related cell death in Friedreich ataxia cells (36, 49). There are possible benefits, particularly cardiac benefits, from GLP-1 agonists but these have not been specifically tested in Friedreich ataxia (40, 41). In the general population, there are benefits related to heart failure from SGLT-2 inhibitors (43), but this has not been tested in Friedreich ataxia. If one were to utilize a SGLT-2 inhibitor, ketone monitoring and close-follow up with endocrinology based on risk of euglycemic diabetic ketoacidosis (DKA) is necessary (44). Despite limited data, in other mitochondrial disorders consideration of GLP-1 agonists or SGLT-2 inhibitors has been recommended by some clinicians, due to favorable cardiac and renal profiles (46).		
Subgroup considerations: This recommendation is for adults with Friedreich ataxia with lower-risk diabetes mellitus (HbA1c <8.5%, no ketones, no acute hyperglycemia).		

Treatment for adults with higher-risk diabetes (HbA1c >= 8.5%, ketones, or acute hyperglycemia)

Should insulin alone versus metformin +/- novel glucose-lowering therapy (e.g., SGLT2i, GLP1RA, DPPIVi) + insulin be used for adults (18y+) with "higher-risk" diabetes mellitus (HbA1c ≥ 8.5%, ketones, or acute hyperglycemia), once stabilized, with Friedreich ataxia?	**Strength**	**Level of evidence***
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 adding 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 Friedreich ataxia and therefore treatment must be individualized. Metformin is used widely, and is used in some cases of Friedreich ataxia-related diabetes. There is a potential risk of lactic acidosis and inhibition of complex I mitochondrial respiratory chain (5, 36). 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 Friedreich ataxia (41, 43). The use of SGLT-2 inhibitors has been associated with euglycemic diabetic ketoacidosis (DKA) (44). Since patients with Friedreich ataxia-related diabetes have decreased insulin secretion, ketone monitoring and close follow-up would be needed if starting an individual with Friedreich ataxia 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).		

Treatment for children with stabilized diabetes mellitus

Should Insulin alone versus metformin +/- novel glucose-lowering therapy (e.g., GLP1RA) + insulin be used for children (under 18 years) with diabetes mellitus, once stabilized, with Friedreich ataxia?	**Strength**	**Level of evidence***
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 Friedreich ataxia-related diabetes mellitus.	↑	⊕◯◯◯
Justification: Children with Friedreich ataxia-related diabetes tend to be more predominantly insulin deficient and therefore require insulin as treatment for diabetes mellitus. Additionally, fewer medications are approved for diabetes management in pediatrics and therefore less is known about their effects, even in "common" forms of pediatric diabetes mellitus.		
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 diabetes, elevated c-peptide while on insulin, elevated BMI, family history of type 2 diabetes, acanthosis nigricans on exam), additional anti-diabetic agents such as metformin or GLP-1 receptor agonists can be considered.		

Lay summary

Lay summary of clinical recommendations for diabetes mellitus in Friedreich ataxia

Why these recommendations?

It is well known that individuals with Friedreich ataxia are at risk of developing diabetes mellitus. Studies have reported prevalence of up to 40% (4 out of 10) of individuals with Friedreich ataxia. However, diabetes may be under-recognized with current screening methods.

Screening: We recommend annual blood tests to screen for diabetes in individuals with Friedreich ataxia. It is important to diagnose diabetes early to avoid significant illness from delayed treatment.

While 2-hour oral glucose tolerance tests may be more sensitive than fasting blood tests for diagnosing diabetes related to Friedreich ataxia, there is not enough evidence at this time to suggest 2-hour oral glucose tolerance tests should be used on a routine annual basis.

Management: Insulin has been used successfully to manage high blood sugars in people with Friedreich ataxia. However, insulin also has undesirable side-effects, including low blood sugar levels.

Other anti-diabetes medications may be considered for people with Friedreich ataxia, in particular those medications that could have other health benefits. Anti-diabetes medications have been shown to be helpful for other people with diabetes, mostly adults, but have not been studied specifically in people with Friedreich ataxia and diabetes. Therefore, an individualized, patient-centered approach to diabetes management in Friedreich ataxia is recommended.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

Your healthcare provider may recommend screening tests for diabetes and discuss symptoms of diabetes such as increased thirst, increased urination, or unintentional weight loss. If you have these symptoms, or questions about diabetes, you should speak to your healthcare provider.

If you are diagnosed with diabetes, your healthcare provider will help you decide on the best treatment for your particular circumstances.

Who are these recommendations specifically for?

Screening recommendations are for all individuals with Friedreich ataxia.

Management recommendations are for individuals already diagnosed with diabetes and are individualized based on age and severity of diabetes.

10.2 Screening and management of osteoporosis in Friedreich ataxia

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10.2.1 Effects of Friedreich ataxia on bone health

Osteoporosis is a skeletal disorder characterized by impaired bone strength. Osteoporosis increases risk of fractures, and is an endemic disease mainly in the elderly (50). In adults, a diagnosis of osteoporosis can be made based upon deficits in bone density alone. By contrast, the diagnosis of osteoporosis in a child requires a history of clinically significant low-trauma fractures (commonly defined as a single vertebral fracture, two long bone fractures before age 10, or three long bone fractures by age 19), with or without a finding of low bone density for age (areal bone mineral density (aBMD) Z-score of -2 or lower for age and sex) (51). Diminished bone loading, due to neuromuscular weakness and/or the inability to tolerate weight bearing activity, is a common cause of impaired bone strength in children and young adults with chronic disease (52, 53). Although individuals with Friedreich ataxia (FRDA) are known to have increased risk for scoliosis and foot deformities, there have been few studies on bone density and risk of fractures in FRDA.

Data from the Friedreich Ataxia Clinical Outcome Measures (FA-COMS) registry showed that 2.1% (23/1104) of people with FRDA reported osteoporosis or osteopenia, and 9.7% (107/1104) reported a fracture, of which none were vertebral/spinal or femoral fractures (54). However, these numbers likely underestimate the prevalence of impaired bone health, since many patients may not have undergone appropriate screening procedures required to identify low bone mineral density.

In one pilot study, bone mineralization was examined systematically in a small study cohort of individuals with FRDA; the prevalence of low bone mineral density was nearly 20% (55). Furthermore, increased severity of ataxia was associated with decreased aBMD of both the femoral neck and lumbar spine, indicating perhaps that ataxia-related decreases in mobility could contribute to decreased bone density. In addition, GAA repeat length, an index of genetic disease severity, was also associated with low bone density, and it may be that the disease itself has adverse impacts on bone health. This study also showed that a majority of individuals with FRDA presented with low 25-OH vitamin D levels (55), which is associated with an increased risk of osteoporosis and fractures (56, 57).

10.2.2 Screening bone health

Adults with Friedreich ataxia

Screening for low aBMD, which characterizes osteopenia and osteoporosis, includes dual-energy X-ray absorptiometry (DXA) and a structured evaluation of fracture history. The mobility status of individuals with FRDA might impact bone mineral density, as demonstrated in a small cross-sectional study where there has been a significantly lower aBMD in the femoral neck (of the hip) in individuals with FRDA who use wheelchairs (55). Measurement of forearm aBMD and/or distal femur could complement traditional assessments in individuals who are mostly non-ambulatory, as these skeletal sites have yielded additional insights in related populations.

Though there is no direct evidence of screening benefit in FRDA, we recommend screening aBMD in adults with FRDA since there are available treatments if low aBMD is identified, and at least one study found a substantial burden of clinically relevant low aBMD in FRDA (55). Radiation exposure during a DXA scan is extremely low and therefore not considered a relevant risk of screening. The

determination of low aBMD and consequently the initiation of an appropriate therapy/prophylaxis could potentially prevent fall-related fractures, and could thus maintain or improve quality of life and prolong capacity for ambulation. While FRDA-specific evidence should be collected, there is persuasive evidence in a range of other populations and conditions for the benefits of osteoporosis therapy, such that opportunities to treat in FRDA should not be missed. In adults with FRDA and osteoporosis, there are a range of approved therapies from which an individualized treatment regimen can be selected by a clinician with relevant expertise.

Children with Friedreich ataxia

No data regarding bone mineralization status or risk of low aBMD in children with FRDA are available. Recent consensus statements (58, 59) highlight the potential utility of DXA in other similar conditions where risk for secondary osteoporosis may be increased, and DXA results may influence treatment decisions. The most appropriate timing for initiation of universal screening is not clear. The utility of universal screening may be lower in individuals with FRDA who have a relatively low burden of comorbidities and minimal limits to ambulation, although there are not yet data to guide this decision. Most appropriate recommendations regarding screening may depend on the age and pubertal status of the child, related imaging results, integrated assessment of fall risk, as well as priorities of patients and families.

In general, risk factors that would support DXA screening in children with FRDA include a clinically significant fragility fracture (long bone or spine), and/or decline in functional status, in particular transition to being mainly non-ambulatory. The frequency of subsequent scans will be guided by degree of aBMD deficit on the initial scan and the clinical scenario (fracture history, ambulatory status, etc.). Per current ISCD guidelines (60), total body less head (TBLH) and lumbar spine (LS) are the standard DXA scan sites in children. In patients with lumbar scoliosis, LS scans will not be accurate and alternate sites should be considered. Hip should be considered in ambulatory adolescents where ongoing need for bone density monitoring into adulthood is expected. Lateral distal femur (if local expertise is available) should be considered in non-ambulatory patients who are anticipated to be at increased risk of distal femur fractures. Forearm scans can also be considered if unable to perform other sites due to factors including scoliosis, contractures, or indwelling hardware. Vertebral fracture assessment by lateral spine x-ray or DXA should be considered in patients with back pain localized to the vertebral column and/or a lumbar spine (aBMD Z-score of -2 or lower), or other suggestive features on DXA (e.g., a lack of expected increase in lumbar spine aBMD).

Screening for low vitamin D

Since vitamin D levels are dependent on several variables (time/season of year at assessment, degree of latitude, activity outdoors) screening might be more widely used in corresponding conditions (e.g., high latitude/low sun exposure, low activity outdoors). Since assessment of vitamin D is done through routine venipuncture and generally available (e.g., during routine laboratory assessments in FRDA, such as glucose, HbA1c) and vitamin D3 supplements (with or without calcium) are widely available, annual assessment of vitamin D (25-OHD) to determine the need for supplementation is warranted, ideally near the end of winter.

10.2.3 Management of low vitamin D, calcium and bone mineral density

Nutritional approaches are reasonable to optimize bone health in individuals with FRDA. Low 25-OH vitamin D levels were present in the majority of the study population in the pilot study described above (55). Since vitamin D deficiency has been associated with an increased risk for osteoporosis

and fractures (56, 57), ensuring adequate intake of vitamin D3, along with calcium for bone mineralization, is appropriate.

With respect to pharmacologic treatment options, although there is no FRDA-specific evidence with respect to the benefit of anti-osteoporotic therapy, the pathophysiology and clinical course of FRDA-related bone disease is likely to be similar to what has been described in other forms of secondary osteoporosis arising from neuromuscular weakness and immobility. Therefore, it is reasonable to assume that evidence supporting the use of bisphosphonates to increase aBMD in children with osteoporosis secondary to conditions including cerebral palsy, spinal muscular atrophy and Rett syndrome may be relevant to the FRDA population (61-64). In addition, in adults with FRDA, the full and rapidly evolving armamentarium of approved pharmacologic therapies for osteoporosis, including anti-resorptive and anabolic agents, should be considered according to individualized assessments by a clinician with relevant expertise.

Best practice statements

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 (58). 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.
Individuals with Friedreich ataxia and osteoporosis should be managed by clinicians with relevant experience.

Recommendations

Screening bone mineral density in adults

Should universal screening assessment (DXA + DXA or other vertebral fracture assessment) versus risk-stratified screening assessment (DXA + DXA or other VF assessment) be used for adults with Friedreich ataxia?	**Strength**	**Level of evidence***
We recommend universal screening assessment of bone mineral density (DXA scan, fracture history) over risk-stratified screening in adults with Friedreich ataxia, given the availability of anti-osteoporosis medications that have been shown to prevent pathological fractures due to low bone mineral density (osteopenia, osteoporosis) in related populations.	↑↑	⊕⊕◯◯
Justification: Although there are no randomized controlled trials, we recommend screening of bone mineral density in Friedreich ataxia since the prevalence of low aBMD might be underestimated and is at least 20% according to a small cross-sectional study (55). Radiation exposure during a DXA scan is extremely low and therefore considered trivial. Determining low aBMD and initiating a corresponding therapy/prophylaxis will potentially prevent fall-related fractures and could maintain or improve quality of life and prolong capacity for ambulation. The initial DXA scan could be ordered by a primary care physician or Friedreich ataxia specialist. If osteoporosis is diagnosed, adults with Friedreich ataxia should be managed by clinicians with relevant clinical experience, such as an endocrinologist.		
Subgroup considerations: This recommendation is for adults with Friedreich ataxia. The mobility status of individuals with Friedreich ataxia might be important in terms of bone mineral density, since in a small cross-sectional study there was a significantly lower aBMD in the femoral neck in		

individuals with Friedreich ataxia who use wheelchairs, probably related to immobility. Measurement of forearm aBMD and/or distal femur could complement routine assessments (spine and hip, as per ISCD 2019 (65)) in individuals who are mostly non-ambulatory as these skeletal sites have yielded additional insights in related populations.

Annual DXA assessment could be considered for individuals found to have low bone density for age on the initial DXA and/or in whom the DXA results would guide further management decisions. The frequency may be adjusted based upon trends in BMD and with input of a bone health specialist. For individuals found to have BMD within the expected range for age, consideration should be given to repeating DXA in 2-3 years, or sooner as indicated by a clinical change (such as change in mobility status, use of new medications that could impact bone health, new fracture history).

Screening bone mineral density in children

Should universal screening (DXA + DXA or other VF assessment) versus risk-stratified screening assessment (DXA + DXA or other VF assessment) be used for children with Friedreich ataxia?	**Strength**	**Level of evidence***
Clinicians should consider universal screening of children with Friedreich ataxia for low bone density via DXA; at minimum, a risk-stratified approach is recommended.	↑	⊕◯◯◯
Justification: Recent consensus statements (58, 59) highlight the potential utility of DXA in other similar conditions where risk for secondary osteoporosis may be increased, and DXA results may influence treatment decisions. The most appropriate timing for initiation of universal screening is not clear. The utility of universal screening may be lower in individuals with Friedreich ataxia who have a relatively low burden of comorbidities and minimal limits to ambulation, although there are not yet data to guide this decision. The initial DXA scan could be ordered by the primary care physician or Friedreich ataxia specialist. If low bone mineral density is diagnosed, children with Friedreich ataxia should be managed by a clinician with relevant clinical experience, such as a pediatric endocrinologist.		
Subgroup considerations: This recommendation is for children with Friedreich ataxia. The most appropriate screening strategy may depend on the age and pubertal status of the child; the longitudinal trajectory of aBMD Z-score and/or absolute aBMD or BMC, DXA and/or related imaging results; an integrated assessment of fall risk; as well as priorities of patients and families. Routine skeletal sites in pediatric DXA scans include the lumbar spine and total body less head (66). Additional sites could be evaluated based on age, clinical history, and local expertise.		

Screening for vitamin D deficiency

Should screening of vitamin D and bone specific markers versus no screening or risk-stratified screening be used for all individuals with Friedreich ataxia?	**Strength**	**Level of evidence***
We conditionally recommend annual screening for vitamin D deficiency over no screening or risk-stratified screening in individuals with Friedreich ataxia.	↑	⊕⊕◯◯
Justification: Since assessment of vitamin D is done through venipuncture and is generally available (e.g., during routine laboratory assessments in Friedreich ataxia such as glucose, HbA1c), along with the wide availability of supplementation with vitamin D, we conditionally recommend assessing vitamin D levels as a basis for supplementation if needed.		

Subgroup considerations: This recommendation is for all individuals with Friedreich ataxia. As vitamin D levels are dependent on several variables (time/season of year during assessment, degree of latitude, activity outdoor), screening might be more widely used in corresponding conditions (e.g., high latitude/low sun exposure, low activity outdoors). Additionally, in individuals found to meet age-specific criteria for osteoporosis, additional screening for markers of bone mineral metabolism could be considered as part of a dedicated bone health evaluation.

Routine calcium and vitamin D supplementation

Should routine calcium and vitamin D supplementation versus selective vitamin D and calcium supplementation be used for all patients with Friedreich ataxia?	**Strength**	**Level of evidence***
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 (58). 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, when indicated, should be individualized. Vitamin D levels can also be used to guide treatment.		

Anti-resorptive therapy in children

Should anti-resorptive therapy versus watchful waiting be used for children (under 18 years) with Friedreich ataxia who may not yet meet osteoporosis criteria but have at least one fragility fracture?	**Strength**	**Level of evidence***
We conditionally recommend anti-resorptive (bisphosphonate) therapy for children with Friedreich ataxia who may not yet have an aBMD Z-score of -2.0 or lower, but have at least one clinically significant fragility fracture. We recommend that treatment be undertaken by a clinician with relevant expertise, such as a pediatric endocrinologist.	↑	⊕◯◯◯
Justification: Although there is no Friedreich ataxia-specific evidence with respect to the benefit of anti-resorptive therapy, Friedreich ataxia-related bone disease likely shares features of other forms of secondary osteoporosis for which there is some available evidence, including from cerebral palsy, Duchenne's muscular dystrophy, and other disorders, particularly inflammatory and/or nutritional. Recent consensus statements (58, 59) emphasize the need for larger and longer-term studies, but recommend consideration of bisphosphonates for two or more long bone fractures and/or one vertebral fracture, the latter being the prototype of a fragility fracture. Additional recommendations are offered stratified by bone DXA Z-score.		

This recommendation is based on the capacity of bisphosphonates to increase aBMD and improve vertebral morphology in other conditions (62). Effects on fracture rate may be present but are difficult to demonstrate. Since bisphosphonate therapy is off-label in pediatrics and has associated risks, both known and unknown, referral to an experienced center is appropriate.
Subgroup considerations: This recommendation is for children with Friedreich ataxia who may not yet have aBMD Z-score of -2.0 or lower, but have at least one clinically significant fragility fracture, where "clinically significant" is defined as a low trauma (fall from standing height or less, at no more than walking speed) fracture of vertebral body, lower extremity long bone, or humerus. The most appropriate treatment recommendations may depend on the age and pubertal status of the child; the longitudinal trajectory of aBMD Z-score and/or absolute aBMD or BMC, DXA and/or related imaging results; an integrated assessment of fall risk; risk of complications from bisphosphonate-related adverse events; as well as priorities of patients and families.

Lay summary

Lay summary of clinical recommendations for osteoporosis in Friedreich ataxia

Osteoporosis (fragile bones) is a skeletal disorder characterized by impaired bone strength. Osteoporosis increases risk of fractures (broken bones). The density of bones can be measured by doing a DXA (dual energy x-ray absorptiometry) scan.

The clinical interpretation of DXA scans varies by age and gender.

- In children and adults under 50 years:
  - Osteoporosis is typically defined by both a low bone mineral density (BMD, Z-score = -2 or lower) and the presence of clinically relevant fragility fracture(s).
  - In the absence of a fragility fracture, a BMD Z-score of -2 or lower is interpreted as "below the expected range for age", and may indicate risk of fracture in the future.
  - A BMD Z-score greater than -2 is interpreted as "within the expected range for age" but does not completely rule out fragility fracture risk.
- In post-menopausal women and men 50 years of age or older:
  - Osteoporosis is defined by a BMD T-score of -2.5 or lower.
  - A BMD T-score between -1 and -2.5 is defined as "low bone density" and may be associated with increased risk of fragility fracture.

Why these recommendations?

Although there is limited information about bone health specifically in Friedreich's Ataxia, we are proposing recommendations based on what is known about risk for impaired bone health in the general population and in individuals with other chronic health conditions.

Screening

For adults with Friedreich ataxia, we recommend universal screening assessment of BMD (using a DXA scan and taking an individual's history of fracture) over screening only those thought to be at higher risk of osteoporosis. This is because available anti-osteoporosis medications have been shown to prevent broken bones due to low bone mineral density in related populations. Therefore, the benefit of screening for low bone mineral density outweighs the very small radiation exposure from DXA scans.

We also suggest screening of children with Friedreich ataxia for low bone health using a DXA scan, or at least screening children thought to be at highest risk of osteoporosis.

The recommendation for bone mineral density screening in children is weaker than for adults because:

1) there are less data on bone disease in children with Friedreich ataxia
2) there are fewer high-quality studies showing the safety and benefits of anti-osteoporosis medications in children
3) using a DXA scan to predict the risk of having a fracture in the future is more complex in children, particularly around the time of puberty.

Vitamin D deficiency has been associated with an increased risk for osteoporosis and fractures. Therefore, universal screening for vitamin D deficiency may be a better option than either no screening or only screening those considered to be at higher risk.

Management of nutritional deficiencies

We suggest addressing low calcium and vitamin D intake from the diet in individuals with Friedreich ataxia, as these are known risk factors for worse bone health and may contribute to longer-term fracture risk.

Management of low bone health

In case of the presence of osteoporosis, treatment of adults with Friedreich ataxia should follow general clinical guidelines.

For children, we suggest that medications called anti-resorptive (bisphosphonate) therapy should be considered for those who have at least one serious fracture that occurred without major trauma.

If possible, treatment should be managed by a clinical team with the appropriate expertise, including an endocrinologist.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

Your healthcare provider may take a thorough history about fractures, your mobility status, and your nutritional status. Since individuals with Friedreich ataxia may be at risk for osteoporosis (fragile bones), your healthcare provider might arrange further investigations, including a DXA scan, a blood test to assess vitamin D levels and possibly other indicators of bone health (for example, calcium levels).

Depending on the results of these tests, calcium and vitamin D supplements and/or a medication might be started, with regular follow-up investigations.

Who are these recommendations specifically for?

Screening recommendations are for all individuals with Friedreich ataxia.

Calcium and vitamin D supplements may be recommended for individuals with Friedreich ataxia who have low vitamin D levels and/or low nutritional intake.

The osteoporosis management recommendations are for those with a diagnosis of osteoporosis or for children with a serious fracture not related to major trauma.

10.3 Assessing nutritional status in Friedreich ataxia

Jaclyn Tamaroff, Andreas Eigentler, David R. Weber, Miriam Cnop and Shana E. McCormack

10.3.1 Nutrition and Friedreich ataxia

While there are limited data specifically related to Friedreich ataxia (FRDA), ensuring optimal nutrition is critical for any individual with a chronic medical condition. Body mass index (BMI) is frequently used in clinical practice to screen for undernutrition or over-nutrition, with specific cut-off values defined by the WHO (67). However, BMI is often missing from visits recorded in the FA-COMS study (5) and individuals with higher modified FRDA Rating Scale (mFARS) scores and/or who are non-ambulatory are less likely to have measurements recorded at visits (68). The reason for neglecting to measure BMI routinely may be due to difficulties in measuring height in individuals with FRDA. In another study, a cross-sectional analysis including anthropometric measurements in FRDA (n=158, 109 adults, 49 children) found that 20% of children were underweight, with BMI at or below the fifth percentile (3). Similarly, baseline characteristics in the FACOMS reported that 17% of children (42/253) were underweight and 33% of adults (105/317) were overweight or obese (BMI ≥ 25 kg/m^2) (68). A smaller study reported that 7/16 individuals with FRDA were overweight and 1/16 was severely obese (14).

10.3.2 Body mass index thresholds

BMI may not be the optimal reflection of body composition (7), particularly when compared to results from detailed assessments typically available in the research setting; however, measuring BMI is a practical way to perform an initial screen for nutritional status in a clinical setting. Standard BMI thresholds, as defined by the WHO or country specific, that are used in the general population are also used in individuals with other disorders impacting the mitochondria. For example, one report using BMI notes a high prevalence of undernutrition in children with genetic mitochondrial diseases, and also a substantial prevalence of overweight or obesity in adults with the same disorders (69, 70). Therefore, we recommend assessing BMI annually in individuals with FRDA. We also suggest beginning with reference BMI thresholds to screen for underweight and overweight/obesity, recognizing that neither the extent to which BMI reflects body composition nor the clinical relevance of BMI are well characterized in FRDA.

While data are limited in FRDA, higher BMI increases the risk of diabetes and other cardio-metabolic disorders in the general population (71, 72). As diabetes and cardiomyopathy are known co-morbidities in FRDA, it is important to counsel patients on healthful nutrition and how to undertake exercise safely. Beyond the associated risks for health problems, elevated BMI may also make mobility and transfers more difficult. With respect to nutritional interventions, individuals who are overweight and/or individuals with specific FRDA-related co-morbidities (e.g., diabetes, cardiomyopathy) for which nutrition is an established part of management, should receive appropriate counseling. As with any child identified to be underweight, children with FRDA who are underweight should be evaluated by a multidisciplinary team with clinical expertise in nutritional management. Currently, there is no specific evidence in support of management practices of underweight children with FRDA.

Best practice statements

All individuals with Friedreich ataxia should have height, weight, and BMI measured at least annually. In the minority of individuals who cannot safely stand with assistance, an alternate measurement could be used (e.g., ulnar length, supine length, seated height, or arm span).
The United States Preventive Services Task Force (USPSTF) and other organizations recommend routine screening for nutritional status with BMI (in children, adolescents, and adults).

Recommendation

Standard BMI thresholds

Should standard BMI thresholds versus Friedreich ataxia-specific evaluation be used for defining undernutrition and over-nutrition in adults (18 years +) and children (under 18 years) with Friedreich ataxia?	Strength	Level of evidence*
We suggest using standard BMI thresholds to define underweight and overweight in children and adults with Friedreich ataxia.	↑	⊕◯◯◯
Justification: There is no current evidence to suggest that Friedreich ataxia-specific BMI thresholds are needed.		
Subgroup considerations: In children, studies have shown that there is an increased prevalence of being underweight (3) and therefore height and weight should be measured at every clinical or research visit. Standard BMI measurements are used in studies of children with other mitochondrial disorders and low BMI is prevalent (70). While there are limited data on adults with Friedreich ataxia, studies in adults with mitochondrial disease report a high prevalence of being overweight or obese (28% overweight, 20% obese) (69).		

Lay summary

Lay summary of clinical recommendation for assessing nutritional status in Friedreich ataxia

Why this recommendation?

Body mass index (BMI) is a screening tool used to evaluate an individual's nutritional status using height and weight measurements. BMI is often used to indicate whether a person is underweight, normal weight or overweight although it does not always reflect body composition (that is, how much muscle, fat, and bone are present). Despite these limitations, both children and adults should have their height and weight measured annually.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

Your healthcare professional may measure your height and weight at all visits. It might be important to speak to your healthcare professional about your BMI and what this means for you in terms of your nutritional status.

If you have an elevated BMI, your healthcare provider may discuss with you how this could increase your risk for diabetes and heart disease and how this might make mobility and transfers more difficult.

For all individuals with Friedreich ataxia, particularly those with BMI outside the typical range, your healthcare provider may discuss ensuring a balanced and nutritious diet.

Based on your individual comorbidities, such as diabetes or heart failure, your healthcare provider may provide specific nutritional recommendations.

Who is this recommendation specifically for?

This recommendation is for all individuals with Friedreich ataxia.

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