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Risk factors for poor bone health in primary mitochondrial disease

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Abstract

Introduction—Primary mitochondrial disease is caused by either mitochondrial or nuclear DNA mutations that impact the function of the mitochondrial respiratory chain. Individuals with mitochondrial disorders have comorbid conditions that may increase their risk for poor bone health. The objective of this retrospective electronic medical record (EMR) review was to examine risk factors for poor bone health in children and adults with primary mitochondrial disease.

Methods—80 individuals with confirmed clinical and genetic diagnoses of primary mitochondrial disease at the Children's Hospital of Philadelphia (CHOP) were included in this study. Risk factors and bone health outcomes were collected systematically, including: anthropometrics (low BMI), risk-conferring co-morbidities and medications, vitamin D status, nutrition, immobility, fracture history, and, where available, dual energy x-ray absorptiometry (DXA) bone mineral density (BMD) results.

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Authors and contributors

SG created the data abstraction tool in REDCap, collected and analyzed the pertinent data, and created the tables and wrote the first draft of the manuscript. CM and EMM provided data on the genetic and clinical diagnosis of the individuals in the cohort, provided data interpretation, and edited the manuscript. MJF provided data interpretation and edited manuscript. SEM designed the analytic approach, participated in data analysis and interpretation, and edited the manuscript. SEM serves as the guarantor for this article.

Declaration of interest and competing interests

Shifa S. Gandhi declares that she has no conflicts of interest.

Colleen Muraresku declares that she has no conflicts of interest.

Elizabeth M. McCormick declares that she has no conflicts of interest.

Marni J. Falk declares that she has no conflicts of interest.

Shana E. McCormack declares that she has no conflicts of interest.

Ethical guidelines

This study has been approved by the CHOP IRB, and was conducted in accordance with the principles of the Declaration of Helsinki of 1975 as revised in 2000. All written informed consent was obtained from patients and/or guardians, as appropriate.

Results—73% (n=58) had at least one risk factor and 30% (n=24) had four or more risk factors for poor bone health. The median number of risk factors per participant was 2, with an interquartile interval (IQI 0–4). In the subset of the cohort who were known to have sustained any lifetime fracture (n=11), a total of 16 fractures were reported, 6 of which were fragility fractures, indicative of a clinically significant decrease in bone strength.

Conclusions—The prevalence of risk factors for poor bone health in primary mitochondrial disease is high. As part of supportive care, practitioners should address modifiable risk factors to optimize bone health, and have a low threshold to evaluate clinical symptoms that could suggest occult fragility fracture.

Keywords

Mitochondrial diseases; bone mineral density; dual energy x-ray absorptiometry; fracture; osteoporosis; osteopenia

INTRODUCTION

Primary mitochondrial disease is a complex set of conditions characterized by dysfunction of the energy-generating mitochondrial respiratory chain. These conditions can be caused by mutations in either the nuclear or mitochondrial DNA that encodes its constituents or directly impacts its function [1]. Despite considerable variability in clinical presentations, individuals with mitochondrial disease may be at risk for poor bone health, particularly if they are chronically ill, malnourished, and/or immobile. Mitochondrial disease can also increase risk for endocrine conditions that are known to adversely affect bone, including diabetes mellitus, hypoparathyroidism, growth hormone deficiency, and hypogonadism [2] [3], as well as other conditions that increase risk for osteopenia and osteoporosis such as renal tubular acidosis and chronic liver disease.

Currently, our understanding of bone health in mitochondrial diseases is limited, and derives primarily from case studies of children with mitochondrial diseases and compromised bone health. For example, in one such report, a five year old boy with Kearns Sayre Syndrome (KSS) developed rickets with multiple bone deformities and fractures, with bone health that deteriorated to such an extent that he lost the ability to walk [4]. Despite the potential substantial burden of osteopenia and osteoporosis in this population, and the clinical availability of anti-osteoporotic therapies, systematic studies of bone health in mitochondrial disease are lacking [5, 6].

To address this need, and to lay the foundation for future prospective studies, the objective of this retrospective electronic medical record (EMR) review was to examine clinical risk factors for poor bone health in a cohort of individuals with primary mitochondrial disease. In addition, we evaluated key bone health outcomes, including fragility fractures, as well as bone mineral density (BMD), where available, from clinically obtained dual energy x-ray absorptiometry (DXA) scans.

METHODS

Study Design

This was a cross-sectional, observational, retrospective EMR review. Individuals were identified from an ongoing observational cohort study of primary mitochondrial disease at the Children's Hospital of Philadelphia (CHOP). This study has been approved by the CHOP Institutional Review (#08–6177, principal investigator MJF), and written informed consent was obtained from patients and/or guardians, as appropriate. Studies were conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion & Exclusion Criteria

We included all individuals in the parent observational study (n=80/101) who had undergone a clinical evaluation and genetic testing to confirm the diagnosis of primary mitochondrial disease in the context of at least one visit to the CHOP Mitochondrial Disease Clinical Center (Supplementary Figure 1). Inclusion criteria were: i) clinical features consistent with primary mitochondrial disease and ii) molecular genetic evidence of a pathogenic mutation in mtDNA or nDNA in a gene known to be associated with dysfunction of complexes I-V of the respiratory chain [7].

EMR Abstraction

A systematic data abstraction tool was created in a web-based instrument (REDCap). The factors outlined sections that follow were coded as “present”, “absent”, or “missing sufficient data”, for all available information through June 30, 2016. To guide this process, we used the detailed exclusion criteria created for the Bone Mineral Density in Childhood Study (BMDCS), a longitudinal study of skeletal development in healthy children that has been used to generate reference values for bone health in children and adolescents [8].

Demographics

Age, sex, and self-identified race and ethnicity were noted from the participant's most recent visit to CHOP, along with the age at the first CHOP contact and first visit to the CHOP Mitochondrial Disease Clinical Center.

Anthropometrics

Weight, height and body mass index (BMI) from the most recent CHOP visit were noted. In addition, if any of the patients' height, weight and BMI values were ever under the 3rd percentile for age and sex according to Center for Disease Control (CDC 2000) pediatric reference values and/or corresponding adult reference values for underweight, this was noted as well [9]. BMD is affected by extremes of weight [8].

Mitochondrial disease diagnosis

Genetic diagnoses and clinical syndromes were adjudicated by CHOP Mitochondrial Disease Clinical Center genetic counselors (CM, EMM) [7].

Serum 25-OH vitamin D levels

Vitamin D deficiency can be associated with adverse bone outcomes [10]. Participants were identified who had levels below 20ng/ml or 30ng/ml (at either the most recent visit or over all visits), since these thresholds are often used to define deficiency and insufficiency, respectively [11, 12].

Diseases and conditions that predispose to poor bone health

We noted the presence of any chronic conditions known to be associated with poor bone health with a particular focus on: liver disease (acute or chronic), renal disease (renal tubular acidosis, nephrocalcinosis, nephrolithiasis, acute or chronic insufficiency), cancer, diabetes mellitus (DM), thyroid disease, adrenal disease, hypogonadism, and parathyroid disease. We noted nutritional risk factors including: lactose intolerance, chronic gastrostomy or jejunostomy tube feeds, and/or home total parenteral nutrition (TPN) requirement.

Medications that influence bone integrity

For high-risk medications [3, 13–16], we determined whether the patient was: i) currently receiving the medication; ii) had ever received the medication; or iii) had never been noted to receive the medication. For glucocorticoid use, only prolonged (more than 2 weeks), supra-physiologic systemic glucocorticoids were included (i.e., inhaled or topical use steroids were excluded). In addition, recorded history and/or current consumption of nutritional supplements including vitamin D2 or D3 and/or calcium were noted.

Immobility

Ambulatory status, as well as past or current occupational and/or physical therapy were noted.

Fracture history and dual energy x-ray absorptiometry (DXA) findings

The approximate date of the fracture (either retrieved from office visits and/or the date of the diagnostic x-ray), location of fracture, and whether or not it was a traumatic fracture was noted. A fracture was considered traumatic if it occurred because of a high-impact force. A fracture was considered non-traumatic, or a fragility fracture, if it resulted from a force that would not normally cause a fracture, such as a fall from standing height or less [17]. Fractures with unknown etiologies were labeled as such. If DXA scans were available, the T-score for adults and Z-score for children from a reference population based on gender, age and race was recorded [18]. For children, height-adjusted Z-scores for BMD were also calculated to adjust for the known effects of size on BMD measurements [19]. Lumbar spine measurements were evaluated since they provide reproducible measures for BMD in infants and young children, according to the ICSD [20]. In addition, the presence of clinical conditions that could confound DXA results (including scoliosis, kyphosis, and lordosis) as determined either by diagnostic code, physician note, problem list, and/or x-ray result were also noted.

Statistical Analysis

Clinical characteristics were summarized using means and standard deviations or medians and inter-quartile intervals, as appropriate. The number of risk factors for decreased bone health was calculated for each participant. These included: current or past BMI<3rd percentile, high-risk chronic medical conditions or medications, requirement for gastrostomy/jejunostomy tube feedings, lactose intolerance, home TPN, and inability to ambulate independently. If risk factors “overlapped”, e.g., a chronic health problem plus the medication used to treat that chronic health problem, such as growth hormone for growth hormone deficiency, it was only counted once. Detailed fracture information was recorded.

Results

Risk factors for poor bone health

Clinical characteristics are presented in Table 1A and genetic diagnoses are in Table 1B. A summary of the risk factors for poor bone health is presented in Table 2 with additional details in Supplementary Table 1 (25-OH vitamin D levels), Supplementary Table 2 (nutritional considerations and immobility), Supplementary Table 3 (risk factors in the subpopulation with the m.3243A>G mutation) and Supplementary Table 4 (risk factors in the subpopulation with the *POLG* mutations). In addition, we stratified the cohort based on both age and gender and present a summary of the risk factors in Supplemental Table 5. Out of the 80 patients included, 71% (n=57) were pediatric. In the entire cohort, 73% (n=58) had at least one risk factor, 63% (n=50) had at least two risk factors, 41% (n=33) had at least three risk factors, and 30% (n=24) had four or more risk factors for poor bone health. The median number of risk factors per pediatric participant was 2 (IQI 1, 2.5, range 0–8) and per adult participant was also 2 (IQI 0, 2, range 0–6). Almost one-third of the pediatric patients (32%, n=18) and almost half of the adult population (48%, n=11) had a medical condition related to their mitochondrial disease diagnosis that was considered a risk factor for osteoporosis.

With respect to anthropometrics, 6% of the pediatric cohort (3 out of 50 with available current data) had a current BMI less than the 3rd percentile noted and 38% (15 out of 40 pediatric patients with available past data) and 10% (2 out of 21 adult patients) had at least one BMI measurement less than the 3rd percentile noted previously. Notably, 58% (33 out of 56 pediatric patients where feeding type was noted) and 13% (3 out of 23 adults) had an enteral feeding tube in place. With respect to mitochondrial disease subtype, we performed a sensitivity analysis of the 11 patients with the m.3243A>G mutation and found these patients to have a median of 1 risk factor (IQI 0, 2 range 0–3), Supplementary Table 3. We also analyzed patients with the *POLG* mutation and found these patients to have a median of 4 risk factors (IQI 4,4 range 3–5), Supplementary Table 4.

Fractures

Table 3 provides an overview of clinical information from patients who experienced at least one lifetime fracture (n=11), 6 pediatric patients and 5 adult patients. A total of 16 fractures were reported. Seven patients sustained a single fracture, 3 patients had 2 fractures and 1 patient had 3 fractures (this individual was also the only patient in the study to have been

clinically diagnosed with osteoporosis). The prevalence of any noted lifetime fracture in this mixed-age cohort of individuals with mitochondrial disease was 14% (11 out of 80). Six out of 16 fractures were fragility fractures, 6 were traumatic, and in 4, etiology could not be determined. The median age at first fracture was 6.4 years (IQI 5.0–15.4, range 0.3–56). The sites that were fractured most often were the femur, humerus/elbow, and the radius/ulna. On average, these patients had 2.6 risk factors for poor bone health (range 0–8).

DXA

Table 4 provides summarizes results for the 7 individuals (six children, one adult) who underwent at least one DXA scan for evaluation of areal BMD. Five patients underwent one scan, and two patients underwent two scans.

DISCUSSION

In summary, we have demonstrated a high prevalence of risk factors for poor bone health in a cohort of patients with primary mitochondrial disease. As evidence of the impact of this risk, a subset of the cohort also had experienced a fragility fracture, a highly morbid complication of decreased bone health. Despite these findings, only one individual had been prescribed anti-resorptive therapy (one individual with osteopenia was treated with pamidronate).

Over half of this well-curated cohort had at least two clinical risk factors for low BMD. Although this study was not designed to examine the difference between children and adults, we noted that DM is more common in adults (22%) than children (1.8%), and also nutritional factors are noted more commonly in children than in adults (65% versus 17%). Overall, several of these risk factors occurred frequently and deserve additional consideration. For nearly one fifth of the cohort, renal tubular acidosis (RTA) and/or chronic renal insufficiency was present. Even relatively mild acidification defects are associated with decreased bone health [21], thus RTA and/or other metabolic acidosis is a clear risk factor for low BMD. Vitamin D insufficiency (30%) or deficiency (17%) was present in a substantial portion of the cohort in whom levels had been measured (n=30). Abnormal absorption of vitamin D may result from liver or other GI disease, and abnormal vitamin D metabolism can occur in chronic kidney disease. Vitamin D deficiency is also one of many potential mechanisms underlying decreased bone health related to use of some anti-epileptic medications [22]. Vitamin D supplementation was noted explicitly in 23% of the cohort. Since vitamin D deficiency is a modifiable risk factor for poor bone health, vitamin D repletion strategies [23] may require more dedicated attention and individualized titration in this population. In addition, there may be benefits beyond bone to adequate vitamin D levels, including improved muscle oxidative phosphorylation capacity [24]. Diabetes mellitus (DM) is another prominent risk factor for osteoporosis and one of the most common endocrine manifestations of primary mitochondrial disease [25] [26], present in 8% (n=6) of this cohort. Multiple mechanisms have been posited for the association between DM and osteoporosis. For example, the accumulation of advanced glycation end-products can cause osteoblast apoptosis and decrease bone formation [27]. In affected patients, careful DM management, including surveillance for potential effects on bone, is warranted.

Multiple medications increase the risk of osteoporosis [28]. Nearly half of this cohort (45%, n=36) either had taken or were currently taking at least one potentially high-risk medication. Of these, systemic glucocorticoids and anticonvulsants were frequently utilized, 10% (n=8) and 38% (n=30), respectively. Each of these medications has been shown to have deleterious effects on bone turnover [29]. Importantly, abnormal bone turnover may adversely affect bone quality in a manner that is not reflected in BMD as assessed by DXA, but may nonetheless increase the risk of fracture.

Beyond clinical risk factors, there may also be a direct adverse effect of mitochondrial disease at the level of skeletal maturation and bone turnover. Osteoclasts are rich in mitochondria, and energy availability seems to affect their resorptive capacity [30]. The activity of cytochrome c oxidase, complex IV of the mitochondrial respiratory chain, has been shown to regulate the activity of osteoclasts necessary for adaptive bone remodeling [30]. Some insights on the direct effects of mitochondria on bone can also be gleaned from studies in model systems. Mice expressing the defective mitochondrial DNA polymerase (*PolgA*) [31] are models of the corresponding disease in humans. Homozygous knock-in mice with deficient versions of *PolgA* (the catalytic subunit of the mitochondrial DNA polymerase) develop kyphosis and osteoporosis. 6% (n=5) of patients in our cohort had pathogenic mutations in *POLG*. Interestingly, all of these patients had 3 or more risk factors for poor bone health. Specifically, all five patients used enteric feeding tubes, 4 out of 5 were taking anticonvulsants, and 2 had renal disease (Supplementary Table 4). This example illustrates that genetic and/or clinical sub-type may impact the risk for adverse bone health outcomes. There is a basis for this clinical observation in model systems. Specifically, in a mouse model of *POLG*-related mitochondrial disease, osteoblasts were found to have respiratory chain dysfunction and animals had poor bone health [32].

Another approach to understanding the role of mitochondria in bone health is to look for bioenergetic defects in apparently otherwise healthy individuals with pathological fractures. One study examined the mitochondrial genome from blood samples of fifteen men with vertebral fractures and found a novel 3.7 kb mitochondrial DNA deletion, which included genes encoding complex I subunits in the mitochondrial respiratory chain, in two of these patients [33]. It has also been suggested that osteoporosis due to aging could be in part attributable to the accumulation of mitochondrial DNA mutations [34]. In the present study, we are not able to isolate the direct effects of mitochondrial dysfunction on bone from the indirect effects of mitochondrial dysfunction on bone related to comorbidities and medications. However, the growing body of literature on the role of mitochondria in skeletal health, we might expect mitochondrial dysfunction to exert an independent, adverse effect on bone; future studies can address this important issue.

Fractures were sustained by 14% of this cohort. In 55% (n=6 out of 11), the first fracture was noted to occur before age 9 years. The age distribution and exposure profile of any cohort will substantially influence the expected fracture rate, as reflected by age-related fracture incidence values in reference populations [35]. Although to our knowledge there are no other large studies reporting fractures in individuals with mitochondrial diseases, fracture rates can be examined in other conditions for comparison. For example, patients with Friedreich's Ataxia (FRDA), also develop neurological disease, DM, and limited mobility. A

study assessed 28 patients with FRDA and found that 21% (n=6) had a history of bone fracture, and the same percentage had a BMD Z score of -2 or worse [36]. A retrospective study including 221 patients (ages 2–58) documented 42 fractures [37], yielding a similar rate as observed in our present study (42/221, 19% versus 16/80, 20%). Similar to individuals with mitochondrial myopathies, boys with Duchenne Muscular Dystrophy (DMD) have decreased muscle strength that may predispose them to falls, as well as to poor bone health and fractures. One cross-sectional study in DMD (median age 12 years) reported a lifetime fracture rate of 21% [38]. These studies suggest relatively comparable rates of poor bone health and fracture in other conditions.

The excess rate of epilepsy in mitochondrial disease also deserves consideration. Patients with epilepsy have multiple risk factors for osteoporosis and fractures including epilepsy-induced falls, anti-epileptic medications, immobility, low BMI and increased prevalence of endocrine comorbidities including GH deficiency and hypothyroidism [39]. A recent study assessing risk factors for poor bone health in 260 patients with epilepsy (not necessarily related to mitochondrial disease) found that 11% had osteoporosis and 38% (99 of 258 patients) had at least one lifetime fracture [40]. 52% of the 106 patients who had undergone DXA scans had low BMD.

A significant proportion of patients with primary mitochondrial disease were also noted to have a spinal curvature, which may also affect BMD and its clinical assessment. Several studies have found that as spinal curvature increases, BMD decreases [41, 42]. The presence of spinal curvature should be taken into account when considering risk factors for poor bone health.

Anti-resorptive and/or anabolic therapies can be considered for patients with severe osteopenia or osteoporosis. Bisphosphonates are a mainstay of osteoporosis therapy, but there is a limited evidence base in mitochondrial disease, in particular in children. One patient in the cohort was diagnosed with osteopenia, and was started on pamidronate therapy at the age of 13 years, one month after his first DXA scan. This patient received 0.4 mg/kg the first day, and 0.75mg/kg the following day. Four months later, he received 1.1mg/kg. A second DXA scan was performed approximately one year after the third pamidronate infusion, which showed a 29% improvement in lumbar BMD and 8.3% improvement in left femoral neck BMD. The only noted adverse effect was fever after the first infusion. The safety, tolerability, and efficacy of anti-osteoporotic therapies across age and disease subtypes in mitochondrial disease are important areas for future study.

This study has strengths and limitations. We have confined our analysis to genetically defined mitochondrial disorders with rigorously curated clinical data, a clear strength. The study's design was retrospective and cross-sectional, an inherent limitation. We suspect that the true burden of adverse bone outcomes in this cohort may be even higher than the lower limits reported here. Despite this limitation, the present study provides initial estimates of the burden of disease, demonstrates the wide variation in practice with respect to bone health assessment, and provides evidence of opportunities to optimize bone health with supportive measures, including physical activity and nutrition. A summary of clinical considerations

drawn from our study is presented in Table 5 [43–49]. Future studies should evaluate specific strategies to promote bone health in this high-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Synopsis

Patients with primary mitochondrial disease are at increased risk for poor bone health; practitioners should address modifiable risk factors and have a low threshold to evaluate symptoms suggestive of occult fracture.

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Table 1A

Characteristics of retrospective study primary mitochondrial disease cohort

Number of patients	80
Sex	
Female	59% (47)
Male	41% (33)
Age (y) first assessed by any CHOP physician median, [IQI], (range)	5.9, [0.6, 16.3] (range 0–73)
Patients in each age range (y) at most recent visit:	
0–1.9	13% (10)
2–9.9	30% (24)
10–17.9	29% (23)
18+	29% (23)
Median duration of follow up (y) median, [IQI], (range)	2.0 [0.2, 6.3] (range 0–22)
Number of deceased patients	14% (11)
Self-identified Ethnicity/Race ¹	
White	79% (63)
Hispanic/Latino	10% (8)
Asian	3.8% (3)
Black/African American	3.8% (3)
Other	13% (10)
Unknown/not reported	1.3% (1)

¹Race and ethnicity were ascertained separately.

Table 1B

Genetic diagnoses of primary mitochondrial disease cohort

Mitochondrial DNA mutations (mtDNA gene)	Clinical Diagnosis	Number of patients
tRNA ^{LEU}	MELAS	11
Deletion	CPEO KSS	1 5
ND1	LHON	4
ATP6	Multisystem disease	4
tRNA ^{TRP}	Multisystem disease	3
ND5	Leigh Syndrome	3
ATP8	Multisystem disease	3
tRNA ^{LYS}	MERFF	2
ND3	Leigh Syndrome	2
ND4/ND6	Multisystem Disease	2
tRNA ^{SER}	Multisystem Disease	1
tRNA ^{PHE}	Multisystem Disease	1
tRNA ^{VAL}	MELAS	1
ND4	LHON Leigh Syndrome	1 1
Total	N=45	
Nuclear DNA mutations (gene)	Number of patients	
POLG	5	
BCORL1	2	
DES	2	
FBXL4	2	
MFN2	2	
MPV17	2	
RMND1	2	
SLC25A12	2	
ANT1	1	
C12orf65	1	
COQ4	1	
DLD	1	
ETFB	1	
HSD17B10	1	
MRPL3	1	
NDUFS1	1	
NDUFS8	1	
OPA1	1	
PEPCK	1	

Mitochondrial DNA mutations (mtDNA gene)	Clinical Diagnosis	Number of patients
POLG2		1
RARB		1
RRM2B		1
SURF1		1
TWINKLE		1
Total		N= 35

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Table 2

Risk Factors for Bone Health

	Pediatric (n=57)	Adult (n=23)	Total (n=80)
Patients with at least one risk factor:	75% (n= 43)	65% (n=15)	73% (n=58)
Patients with at least two risk factors:	65% (n= 37)	56% (n=13)	63% (n=50)
Patients with at least three risk factors:	47% (n= 27)	26% (n=6)	41% (n=33)
Patients with more than three risk factors:	37% (n= 21)	13% (n=3)	30% (n=24)
Median [IQ]:	2 [1,2,5]	2 [0,2,5]	2 [0,4]
Range:	(0–8)	(0–6)	(0–8)
High-risk medical conditions (aside from primary mitochondrial disease)			
Any high-risk condition	32% (18)	48% (11)	36% (29)
Kidney Disease (acute, chronic, RTA)	23% (13)	4.3% (1)	18% (14)
Liver Disease (acute, chronic, elevated liver enzymes)	12% (7)	9% (2)	11% (9)
Diabetes Mellitus	1.8% (1)	22% (5)	7.5% (6)
Thyroid Disease	7% (4)	9% (2)	7.5% (6)
Gonadal Disorder	3.5% (2)	17% (4)	7.5% (6)
Adrenal Disorder	9% (5)	0	6.3% (5)
Parathyroid Disorder	1.8% (1)	0	1.3% (1)
Cancer	0	4.3% (1)	1.3% (1)
Current or previous exposure to high-risk medications			
Any exposure to high-risk medication	46% (26)	43% (10)	45% (36)
Anticonvulsants	39% (22)	35% (8)	38% (30)
Systemic Glucocorticoids	12% (7)	4.3% (1)	10% (8)
Growth hormone	3.5% (2)	9% (2)	5.0% (4)
Loop Diuretics	1.8% (1)	9% (2)	3.8% (3)
Nutritional factors			
Any nutritional factor	65% (37)	17% (4)	51% (41)
BMI below third percentile			
Current ¹	6% (3)	0	4.1% (3)
Past ²	32% (15)	10% (2)	28% (17)

	Pediatric (n=57)	Adult (n=23)	Total (n=80)
Use of G/J tube ³	58% (33)	21% (3)	46% (36)
Home TPN ⁴	11% (6)	0	7.7% (6)
Lactose intolerance	12% (7)	0	8.8% (7)
Physical activity			
Wheelchair bound ⁵	31% (17)	38% (8)	32% (25)

¹ Current BMI values not available in 6 pediatric patient and 1 adult patient.

² Past BMI values not available in 10 pediatric patients and 9 adult patients.

³ Feeding status unclear in 1 pediatric patients.

⁴ Home TPN status unclear in 2 pediatric patients.

⁵ Ambulatory status unknown in 2 pediatric patients and 2 adult patients.

Table 3

Mitochondrial disease patients with a lifetime history of any fracture.

ID	Sex	Age at fracture (y) Fracture location Traumatic (T)	Mitochondrial Disease (Clinical & gene defect)	Risk Factors-conditions	High Risk Medications	Nutritional factors	Other Factors
1	F	14.9 r. humerus/elbow Not traumatic 14.9 r. radius/ulna Not traumatic 14.9 l. humerus/elbow Not traumatic	Other RMND1	Osteoporosis Renal failure Adrenal disorder Hypothyroidism	Anticonvulsants	BMI was less than 3 rd percentile 25-OHD<20 ng/mL G/J tube Home TPN Took Vit D supplementation in past	Scoliosis & kyphosis Non-ambulatory
2	F	2.7 r. femur Not Traumatic 2.8 l. femur Not Traumatic	Leigh Disease Complex I deficiency Lactic acidosis NDUFS8	RTA	Anticonvulsants	25-OHD<20 ng/mL in past G/J tube	Kyphosis & lordosis
3	M	5.1 r. femur Unknown 7.4 r. femur Unknown	Multisystem Disease tRNA ^{SER}	DM Hypogonadotropic hypogonadism	GH Loop diuretics	BMI was less than 3 rd percentile	Scoliosis Non-ambulatory
4	M	5.0 l. radius/ulna traumatic 8.7 l. toe Traumatic	Mitochondrial cytopathy Lactic acidosis ATP6	NA	NA	NA	Utilizes assistive walking device
5	F	5.6 r. humerus/elbow Traumatic	Leigh Disease Mitochondrial cytopathy ND3	NA	NA	Current BMI less than 3 rd percentile 25-OH D<30 ng/mL recent	NA
6	F	7.1 r. finger/thumb Traumatic	MELAS tRNA ^{LEU}	NA	Past glucocorticoid use Anticonvulsants	Taking calcium & vit.D	NA
7	F	0.25 Face/skull Traumatic	Leigh Syndrome ND5	NA	NA	BMI was less than 3 rd percent 25-OH D<30 ng/mL in past G/J tube	NA
8	F	15.6 Left Skull/face Traumatic	Complex IV deficiency tRNA ^{TRP}	NA	NA	NA	NA
9	M	36.9 Rib/sternum Not Traumatic	CPEO OPA1	Hyperthyroidism	NA	25-OHD<20 ng/mL	Non-ambulatory
10	F	56.3 l. humerus/elbow Unknown	MELAS tRNA ^{LEU}	NA	Anticonvulsants	G/J tube	Non-ambulatory
11	F	NA foot unknown	Other MFN2	PCOS	Anticonvulsants	NA	NA

5 out of 11 patients had taken or were currently taking anticonvulsant medication, 4 out of 11 had a G/I tube, 5 out of 11 had at least one 25-OHD level noted to be below the specified thresholds, 5 out of 11 patients utilized an assisted walking device, and 2 out of the 11 patients were noted to have been taking or currently taking vitamin D supplements.* exact date of fracture unknown, date of x-ray was used to calculate age; ** none of these patients had undergone a DXA scan.

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Table 4

Mitochondrial disease patients who had DXA scans.

Sex	Age at DXA scan (y)	DXA Z score (lumbar spine) HAZ adjusted Z score	Mitochondrial Disease (Clinical & gene defect)	Risk factors-conditions	High risk Medications	Nutritional factors/activity	Other
F	4.6	-0.4; HAZ NA ¹	Mitochondrial cytopathy Lactic acidosis RMND1	Renal disease	Anticonvulsants	BMI<3 rd percentile in past G/J tube	NA
M	7.8 9.0 (second scan)	-0.65 -0.73 (second scan) HAZ -0.38 -0.52 (second scan)	Mitochondrial cytopathy ATP6	NA	NA	BMI<3 rd percentile in past 25-OHD<30 ng/mL Lactose intolerant G/J tube	Non-ambulatory
M	8.3	-1.48; HAZ -0.89	Mitochondrial DNA depletion POLG	Adrenal disorder	Glucocorticoid Anticonvulsant	25-OHD<20 ng/mL past G/J tube Taking vit D & calcium	Kyphosis, lordosis
M ²	13 14.5 (second scan)	-2.5 -1.9 (second scan) HAZ -0.64 -0.20 (second scan)	Multisystem Disease HSD17B10	NA	Anticonvulsant	G/J tube	Scoliosis, kyphosis Non-ambulatory
M	12.2	-1.06; HAZ 1.35	CPEO KSS Lactic acidosis mtDNA deletion	Renal disease Hypothyroidism	GH in past and discontinued	25-OHD<20 ng/mL past Taking vit D	NA
M	17	0.8 ³ HAZ unknown	Other ETFB	Liver disease	Anticonvulsants	G/J tube Home TPN Taking vit D	Prematurity
M	60	T score unknown	CPEO TWINKLE	Gonadal disorder	NA	Taking vit D	Scoliosis, kyphosis

¹ Height adjusted DXA only applicable to 5–20 year old.

² This patient was diagnosed with osteopenia and received pamidronate therapy after the first DXA scan.

³ Height adjusted could not be calculated since DXA lumbar spine BMD not available.

Table 4 summary: The median lumbar spine Z score (not adjusted for height) for the first DXA of the six patients was -0.86 (IQR, -1.38, -0.46, range, -2.5, 0.8). The median height adjusted z-score of the first DXA scan for available values was -0.51 (IQR, -0.70, 0.05, range, -0.89, 1.35). None of these patients had sustained a fracture.

Table 5

Important recommendations for clinical care of patients with primary mitochondrial disease

<ul style="list-style-type: none"> • Diagnosis of osteopenia and osteoporosis in adults with mitochondrial disease is the same as in the general population. For children, The International Society for Clinical Densitometry (ISCD) has proposed that the diagnosis of osteoporosis should be made based on: i) a size-corrected BMD z-score of more than 2 SD below the mean and ii) a "significant fracture history"^I resulting from mild or moderate trauma.
<ul style="list-style-type: none"> • DXA scans should be considered in patients at risk for poor bone health when results would alter clinical management, e.g., influence a decision to pursue anti-osteoporotic therapies. In particular in children, height-adjusted DXA Z-score should be used when applying ISCD criteria.
<ul style="list-style-type: none"> • Clinicians should be aware that the development of new and suggestive symptoms that could be related to an occult fracture. For example, vertebral compression fractures caused by osteoporosis or low BMD can lead to back pain and/or progressive kyphosis.
<ul style="list-style-type: none"> • Optimizing nutritional status, including treatment of vitamin D deficiency should be a part of the clinical care of all patients with mitochondrial diseases.
<ul style="list-style-type: none"> • A consensus statement from the Mitochondrial Medicine Society includes a recommendation that a combination of resistive and progressive exercise, with supervision, is indicated for patients with mitochondrial diseases. Exercise and/or physical therapy will improve muscle strength and coordination, which may prevent future falls and resulting fractures.

^IDefined by the ISCD as: 2 or more long bone fractures by age 10 years, or 3 or more long bone fractures by age 19 years.