REVIEW

Management of Bone Disease in Gaucher Disease Type 1: Clinical Practice

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ABSTRACT

Gaucher disease is a rare autosomal recessive disorder of glycosphingolipid metabolism resulting from deficient activity of the lysosomal enzyme beta-glucocerebrosidase that causes accumulation of glucosylceramide in tissue macrophage with damage to hematological, visceral, and skeletal organ systems. Severity and progression may vary independently among these domains, necessitating individualized therapy. Skeletal involvement is highly prevalent and often associated with intense pain, impaired mobility, and reduced quality of life. Enzyme replacement therapy improves parameters in all affected domains, but skeletal involvement requires longer treatment and higher dosages to obtain significant results. Despite numerous papers on bone complications in patients with Gaucher disease, there are no specific indications on how to assess properly bone involvement in such condition, the frequency

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of assessment, the use of markers for osteoblast and osteoclast activity, or the administration of bisphosphonates or other symptomatic drugs in adult and pediatric patients. Starting from a re-evaluation of cases with bone involvement, we have identified some common errors in the diagnostic approach and management. The aim of this paper was to propose a methodological and critical approach to the diagnosis, follow-up and treatment of bone disease in patients with Gaucher disease type 1.

INTRODUCTION

Gaucher disease (GD; OMIM #230800) is a rare autosomal recessive hereditary disorder of glycosphingolipid metabolism resulting from deficient activity of the lysosomal enzyme β-glucocerebrosidase (EC 3.2.1.45; lysosomal glucocerebrosidase). Glucosylceramide accumulates in macrophages (Gaucher cells) in the spleen, liver, and bone marrow. Although GD has a continuous spectrum of severity, it is traditionally classified into three forms: type 1 (chronic; lacking early onset neuronopathy), type 2 (acute; with early onset neuronopathy), and type 3 (chronic; with early onset neuronopathy) [1]. Type 1 GD accounts for the vast majority of cases, with an incidence of approximately 1/40–60,000 in the general population [2, 3] and 1/500 in the Ashkenazy population [4].

GD type 1 is a chronic multi-organ disorder with a variety of signs and symptoms that include hepatomegaly, splenomegaly, (pan)cytopenia, pulmonary disease, and various bone manifestations. The severity and clinical course of the disease are extremely heterogeneous, varying between patients and affected domains in the same patient [1]. Bone pathology in GD affects both the marrow and structural compartments, although the precise pathophysiological mechanisms are not yet well understood. Bone marrow infiltration by Gaucher cells may cause vascular occlusion, ischemia, and compression, whereas mineralization defects may result from abnormal bone remodeling [1]. Skeletal manifestations are the most disabling long-term complication of GD, and more than 80% of patients have signs of bone involvement at diagnosis [5, 6]. These may include abnormal bone remodeling, osteopenia, lytic lesions, pathological fractures, vertebral collapse, and avascular osteonecrosis—particularly at the femoral or humeral heads—with possible bone collapse and joint involvement [7]. Osteopenia is common in patients with GD, and often occurs early in life, resulting in reduced bone mineral density (BMD) with lower peak bone mass and increased risk of complications associated with bone fragility [8].

Skeletal involvement is a compelling indication for enzyme replacement therapy (ERT) and some bone parameters are key treatment goals [8, 9]. While patients with bone pain and bone crisis resulting from bone marrow infiltration generally respond to ERT within 2 years [10], improvement of bone mineral density (BMD) is markedly dose-dependent and requires up to 8 years of high-dosage therapy to normalize [11]. Some bone manifestations are irreversible [12]; thus, early and sustained treatment is critical. Adequate treatment is especially important during adolescence and early adulthood, when peak bone mass is accrued [13]. Moreover, early treatment may reduce the risk of avascular bone necrosis [14]. Over time, impaired quality of life (QoL) may become refractory to

therapy due to the occurrence of permanent bone sequelae and the need for joint replacements [15, 16].

Guidelines have been elaborated for the diagnosis, treatment and follow-up of patients with GD [17, 18]; however, detailed information on the correct evaluation and interpretation of skeletal involvement are lacking. The aim of this paper was to propose a methodological and critical approach to the diagnosis, follow-up, and treatment of bone disease in patients with GD type 1.

METHODS

To address the unmet need for improving the approach to bone disease in GD, a panel of physicians with experience in GD diagnosis and treatment, as well as an expert on bone disease, convened three times to review the literature, discuss clinical cases of GD with various forms and presentations of bone involvement, and formulate recommendations for diagnosing, monitoring, and treating skeletal manifestations of GD. Starting from a re-evaluation of cases with bone involvement, we have identified some common errors in the diagnostic approach and management.

The analysis in this article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CASE REPORTS

Three cases of GD are presented to illustrate situations encountered in clinical practice; several common pitfalls are highlighted (Supplement 1). Suboptimal outcomes in these clinical cases can be attributed to (a) late diagnosis of GD, (b) the improper use or interpretation of imaging methods for the diagnosis and monitoring of skeletal involvement, or (c) inadequate ERT dosage. Based on these observations we reconsider the most important methods for evaluating bone disease in GD and make critical suggestions for their use and interpretation in light of recent advances in osteoporosis.

DISCUSSION

Imaging Methods for Assessing Bone Damage

Dual Energy X-ray Absorptiometry (Table 1)
The gold standard for quantitative assessment of bone mineral status in adults is dual energy X-ray absorptiometry (DXA), performed at the lumbar spine (L1–L4) and hip (total hip or femoral neck). In children, in addition to DXA performed on the L1–L4 lumbar vertebrae, scans of the total body less head (TBLH) are mandatory, whereas measurement of BMD at the femur is not recommended due to high variability in skeletal maturity [19]. The parameters obtained from these measurements are bone mineral content (BMC) in grams, area in cm^2, and BMD in g/cm^2. Because of the two-dimensional nature of DXA, measurements are strongly influenced by bone size, skeletal maturity, and pubertal stage. Small bones may lead to an underestimation of BMD. Other confounding factors include avascular necrosis of the proximal femur and vertebral fractures, which may provide misleading results. In adults, the presence of osteophytes, vascular calcifications, and calculi can lead to overestimation of bone mass.

The reference DXA parameter for premenopausal women, for men younger than

Table 1 Key points for using dual energy X-ray absorptiometry (DXA) for diagnosis and follow-up in patients with Gaucher disease (GD)

Procedure

The essential parameters are bone mineral content in grams, bone area (cm^2), and bone mass density (BMD) (g/cm^2)

Serial measurements of BMD should be performed with the same equipment and, if possible, by the same operator

Sites to examine

Lumbar spine (L1–L4)

Total body less head (TBLH)

Proximal femur (total hip and femoral neck)

When these sites cannot be measured, the distal third of the radius of the non-dominant forearm is evaluated

Interpretation

DXA should be interpreted using the Z-score as a reference value. Z-scores below −2.0 indicate reduced bone mineral density. In postmenopausal women and in men aged ≥50 years the T-score is interpreted using the World Health Organization (WHO) classification for osteopenia/osteoporosis, considering methodological precision and least significant change detectable

Frequency

DXA should be performed at baseline and after 12 months in untreated asymptomatic patients and in patients who have not reached therapeutic goals on enzyme replacement therapy (ERT). When therapeutic goals are achieved, the guidelines recommend follow-up every 12–24 months. However, in our experience this can be carried out every 36 months, in the absence of inter-current conditions associated with BMD loss

Recommendations for pediatric patients

DXA is performed in patients aged ≥5 years with scans of the lumbar vertebrae (L1–L4) and TBLH; measurement of BMD at the femur is not recommended. Results are interpreted with the Z-score

50 years old, and for the pediatric population is the Z-score, which refers to the mean BMD of the subject compared to a population of similar age, sex, and ethnicity [20]. In the aforementioned populations, DXA measurements with a Z-score less than or equal to −2.0 should be reported as "BMC or BMD below the expected range for chronological age" and not with the term "osteopenia" [21], whereas the diagnosis of osteoporosis should not be based only on BMD values. For postmenopausal women and men aged ≥50 years, the preferred parameter is the T-score, which expresses BMD compared to that of young adults (aged 20–29 years) of the same sex. It should be interpreted according to the World Health Organization densitometric classification, in which a T-score between −1.0 and −2.5 indicates osteopenia, while a T-score less than −2.5 indicates osteoporosis.

How to Perform DXA Measurement of BMD at the lumbar spine should be performed in the anteroposterior projection, considering the mean BMD of at least two vertebrae among L1–L4, excluding any vertebrae with defects or artifacts. The femoral neck or total hip is the optimal site for fracture risk assessment [22]. In certain circumstances (e.g., for very obese patients or the presence of bone damage in

vertebral or femoral sites), a different skeletal site may be used, such as the distal third of the radius in the non-dominant arm. The minimum age for densitometric examinations is 5 years.

Regarding methodological variability and the accuracy of measurements, the precision error and least significant change (LSC) detectable must be determined for each DXA apparatus, independently from the information provided by the manufacturer. Strict adherence to protocols is required to obtain accurate results. For complete instructions, refer to appendix II of the International Society for Clinical Densitometry (ISCD) 2013 position document [20]. Equipment accuracy must be assessed on a representative sample of patients at any clinic. To analyze precision, 3 measurements must be performed on each of at least 15 patients or 2 measurements on 30 patients, repositioning the patient after each scan. The minimum acceptable precision varies depending on the anatomical site evaluated, in particular, for the lumbar spine it is 9%, corresponding to an LSC of 5.3%. This margin of error should be taken into account for repeated measurements performed to assess the effectiveness of drug treatment. For example, a 4% variation in BMD of the lumbar spine after a year of therapy would be below the LSC for this segment (5.3%). Therefore, the increase in density would not be attributable with certainty to a pharmacological effect. Serial evaluations should consider not only the Z-score (or T-score) and BMD but also the BMC and the area.

Frequency of DXA Follow-Up Current recommendations indicate that DXA should be performed at baseline and after 12–24 months in untreated patients with GD and in those who have reached therapeutic

Table 2 Key points for the use of MRI to assess bone marrow infiltration (BMI) in the diagnosis and follow-up of patients with GD

Procedure and interpretation

T1-weighted MRI can measure the marrow fat component; sequences of the femur and spine are used for the quantification of bone marrow infiltration

T2-weighted sequences are used to identify bone infarcts, osteonecrosis, and the differential diagnosis of bone crises. Evaluation of avascular osteonecrosis requires T2-weighted MRI sequences and short-tau inversion recovery (STIR)

The same semi-quantitative assessment method should be used at baseline and follow-up

Frequency

Current recommendations indicate that MRI should be performed at baseline and repeated every

12–24 months in treated patients with normal scores

24–36 months in untreated patients with normalized scores

12 months in patients with severe bone marrow burden (BMB) scores

24 months for patients with moderate BMB scores

Time dosage is adjusted when significant complications occur

However, we suggest that follow-up may be performed every

12 months if the normalized score is >1

24 months if the normalized score is ≤1

36 months in stable patients with good metabolic control and normalized scores consistently ≤1

Time dosage is adjusted, or significant complications occur

Recommendations for pediatric patients

Age-related bone marrow conversion in children interferes with evaluation of infiltration; currently there are no guidelines or standardized methods for analyzing this parameter

goals on ERT, whereas patients who have not reached therapeutic goals should be assessed every 12 months [17]. However, given the slow rate of BMD changes we suggest that assessment can be performed every 24–36 months in untreated patients, and every 36 months in patients who have achieved goals for skeletal involvement on ERT. DXA should be repeated at shorter intervals (e.g., 12–24 months) in patients with conditions associated with a rapid loss of bone mass (e.g., corticosteroids therapy). The minimum time interval for evaluating bone density during the course of treatment is 6 months. Serial DXA examinations should be performed using the same device, possibly by the same operator [23].

Magnetic Resonance Imaging (MRI) (Table 2)

Magnetic resonance imaging (MRI) is an extremely sensitive method for monitoring bone pathology in GD. Protocols include T1-weighted spin echo and turbo sequences, short tau inversion recovery (STIR) sequences, as well as T2-weighted spin echo, turbo spin echo or gradient echo sequences. Spin echo MRI sequences are useful for identifying bone marrow by its high fat content, which appears as a hyperintense T1-weighted signal and an intermediate-to-hyperintense T2-weighted signal. Bone marrow infiltration (BMI) by Gaucher cells displaces fatty marrow, resulting in a less intense signal. Regression of BMI, for example as a consequence of ERT, increases marrow fat content and causes the signal intensity to normalize. Some changes are irreversible, such as bone infarction and fibrosis.

MRI is also the most sensitive method to detect osteonecrosis. Increased signal intensity in T1- and T2-weighted images or hyperintense signal in STIR is suggestive of active bone marrow events. STIR may reveal osteonecrosis

that is obscured by Gaucher cell infiltration in T1-and T2-weighted images.

The age-related conversion of hematopoietic to fatty bone marrow that occurs in children interferes with evaluation of BMI, and currently there are no guidelines or standardized methods for analyzing this parameter. Therefore, in clinical practice BMI is not assessed in pediatric patients. However, MRI is useful for assessing osteonecrosis and active bone marrow events in pediatric patients.

MRI is a qualitative method, but semi-quantitative methods have been developed to assess BMI by Gaucher cells. BMI is clinical relevant because it is an index of disease severity and of the risk of bone crisis and osteonecrosis. Semi-quantitative MRI methods compare signal intensities to an internal reference standard. Six semi-quantitative methods have been developed that differ mainly by the body area evaluated. These methods have been validated by comparison to other methods, and inter-rater reliability has been assessed at multiple centers [24–29]. Of these, the bone marrow burden (BMB) seems to be the most commonly used method.

A quantitative MRI method known as quantitative chemical shift imaging (QCSI) has also been developed [30]. QCSI quantifies fat content using differences in the resonant frequencies of fat and water in bone marrow. However, it is not universally available, relies on specialist technical input, is time consuming, and prone to both measurement errors and artifacts. For all these reasons, it is not used in clinical practice. BMI can be measured using scintigraphic imaging with semi-quantitative assessment; however, whereas it is widely available, this method has low specificity, and physiological excretion of markers hampers assessment of the abdominal region. Recently, Di Rocco et al. [3] have normalized these methods so that their

Table 3 Equivalence of disease severity scores for magnetic resonance and scintigraphic evaluation of bone marrow involvement in patients with Gaucher disease

Normalized score	Rosenthal	Dusseldorf	Terk	VDR	BMB
0	0	0	0	>2.0	0–2
1	1–3	1–3	1[a,b]	1.5–2.0	3–7
2	4–7	4–6	2[a,b]	1.0–1.5	8–12
3	8–11	7–8	3[a,b]	<1.0	13–16

Normalized score	QCSI fat fraction	S-MRI	99mTc-sestamibi	99mTc-radiocolloid
0	>0.30	0–4	0–2	Normal
1	0.30–0.25	5–10	3–4	Mild
2	0.20–0.25	11–17	5–6	Moderate
3	<0.20	18–24	7–8	Severe

Reproduced with permission from [3]
[a] The presence of osteonecrosis is not considered in the bone marrow score per se, since it indicates involvement of the bone mineral component rather than the marrow component, which is the primary focus of MRI
[b] Degree of impairment in the normal scintigraphic pattern. *BMB* bone marrow burden, *S-MRI* Spanish magnetic resonance index, *VDR* vertebral disk ratio, *QCSI* quantitative chemical shift index

results are now comparable, allowing clinicians and radiologists to use any one of these methods (Table 3).

Frequency of MRI Follow-Up The International Registry Collaborative Gaucher Group (ICGG) has developed recommendations for effective monitoring of adult patients with GD type 1 [17]. These indicate that MRI should be performed at diagnosis and then every 12–24 months for patients not receiving ERT and for those who have not achieved therapeutic goals while receiving ERT, whereas patients who have achieved therapeutic goals while receiving ERT should be monitored every 24–36 months. Assessments should be performed also when changing therapy or in the event of significant clinical complications. Therapeutic goals for BMI have not been established.

Follow-up imaging may be less frequent in untreated patients with minimal disease who lack evidence of progression over several years, or in treated patients with negligible BMI and evidence of stable disease. Conversely, evaluations should be more frequent in untreated symptomatic patients with significant disease burden [17].

MRI is cost-effective in terms of diagnostic value and the cost of therapy; however, it is expensive and for this reason, we propose the following protocol. At baseline, total body semi-quantitative MRI should be used to check for osteonecrosis in sites other than the femoral head [31]. The same semi-quantitative method should be used for follow-up. However, in our opinion, total body MRI is not useful for follow-up. Instead, we suggest performing MRI on specific symptomatic regions.

If the baseline normalized score (see Table 2) is ≤1, MRI should be performed every 24 months; if it is >1, MRI should be performed every 12 months. In stable patients with good metabolic control and scores

consistently ≤1, MRI can be performed every 36 months.

Plain Radiography

Radiographic examination is widely available and inexpensive, but it has low sensitivity in detecting initial and small changes in skeletal involvement in GD patients [7]. However, it is useful for detecting bone complications such as fractures. In addition, radiographic imaging may reveal skeletal lesions, cortical bone thinning, and Erlenmeyer flask deformation that may lead to incidental diagnosis of GD in asymptomatic patients.

The guideline developed by the International Collaborative Gaucher Group (ICGG) recommends that the initial assessment include X-ray examination of the femora, spine, and any other symptomatic sites, but indicates that MRI provides much more information on BMB [17]. Conventional radiography may be useful for characterizing osteonecrosis of the proximal femur and osteosclerotic areas, when used in the context of an appropriate classification system.

Steinberg has proposed a classification system that we agreed is useful for identifying progression of radiographic damage and providing information to guide surgical approaches (Steinberg et al. 1998). It is derived from the system of Arlet and Ficat [32] and includes additional stages (Table 4).

Biomarkers for Bone Damage

Bone manifestations commonly involve decreases or increases in the rate of bone turnover and imbalance between bone resorption and formation. Bone turnover can be measured with specific biochemical markers

Table 4 Steinberg (or University of Pennsylvania) classification system for avascular necrosis of the femoral head

Stage	Criteria
0	Normal or nondiagnostic radiograph, bone scan, MRI
I	Normal radiographs; abnormal bone scan and/or MRI
	A: Mild (<15% of femoral head affected)
	B: Moderate (15–30%)
	C: Severe (>30%)
II	Cystic and sclerotic changes in femoral head
	A: Mild (<15% of femoral head affected)
	B: Moderate (15–30%)
	C: Severe (>30%)
III	Subchondral collapse (crescent sign) without flattening
	A: Mild (<15% of articular surface)
	B: Moderate (15–30%)
	C: Severe (>30%)
IV	Flattening of femoral head
	A: Mild (<15% of surface and <2 mm depression)
	B: Moderate (15–30% of surface and 2–4 mm depression)
	C: Severe (>30% of surface and >4 mm depression)
V	Joint narrowing or acetabular changes
	A: Mild[a]
	B: Moderate[a]
	C: Severe[a]
VI	Advanced degenerative changes

[a] Mean femoral head involvement, as determined in stage IV, and estimated acetabular involvement. *MRI* magnetic resonance imaging. Reproduced with permission from [60]

Table 5 Biomarkers for bone damage

We suggest that the following markers be measured every 12 months
Serum calcium and phosphorus
Urinary calcium and phosphorus
The bone isoenzyme of alkaline phosphatase (BALP)
Parathyroid hormone
25-Hydroxyvitamin D
In addition, vitamin D status should be determined and corrected if deficient

for enzyme activities, the release of various structural components of bone, and proteins involved in the processes of bone formation (Table 5). Over the years, most of these parameters have been tested in patients with GD [33–40]. Urinary total hydroxyproline levels are used to identify osteoclastic hyperactivity. Stowens et al. [41] reported a reduction in urinary hydroxyproline levels in about one-third of patients with GD compared with controls, suggesting a reduction in bone resorption in these patients. Furthermore, osteoblast activity also appears to be suppressed in patients with GD not treated with replacement therapy, as demonstrated by a threefold decrease in levels of markers of osteoblast activity: osteocalcin [34] and carboxy-terminal propeptide of procollagen type 1 (P1NP) [35]. More recently, Van Dussen et al [40]. reported a significant reduction in osteocalcin levels, without significant changes in levels of carboxy-terminal telopeptide of type I collagen (CTX, a marker of osteoclast activity), in 50% of patients with GD type 1, suggesting that the altered bone turnover is mainly characterized by a reduction of bone formation. Moreover, Mikosch et al. [38] had previously reported that levels of tartrate-resistant acid phosphatase (TRAP), a widely used osteoclast marker, are unchanged in patients with GD.

Recently, a systematic review has consolidated the view that there are many contradictory results in the literature and that currently there is no scientific evidence to support the use of biochemical markers for the early diagnosis or follow-up of bone involvement in GD [42]. CTX and P1NP have gained attention recently; however, there is not sufficient evidence to warrant their use in clinical practice. It is not clear that any of these markers provide information on bone involvement beyond that obtained with the routinely measured indicators of bone metabolism. Furthermore, biochemical markers provide only an instantaneous measurement of status, whereas imaging reflects the cumulative effects of bone gain and loss throughout life. Thus, we recommend periodic measurement of serum calcium and phosphorus, bone isoenzyme of alkaline phosphatase (BALP), PTH, urinary calcium and phosphorus, and 25-hydroxyvitamin D. In addition, because vitamin D deficiency is common, its status should be determined and corrected if needed.

Enzyme Replacement Therapy

The availability of enzyme replacement therapy (ERT) has significantly improved the treatment of GD, making it possible to establish meaningful therapeutic goals for skeletal manifestations of GD (Table 6). Three recombinant mannose-terminated forms of glucocerebrosidase are available for ERT: imiglucerase [43] was approved in 1994, velaglucerase alfa [44] was approved in the US and Europe in 2010, and taliglucerase alfa [45] was approved in the US and Israel in 2012, and subsequently in Brazil, Chile, and Mexico. Most of the data on skeletal treatment goals come from studies conducted with imiglucerase, which has been shown to significantly improve all bone parameters identified as therapy goals (Supplementary

Table 6 Key points for enzyme replacement therapy for bone manifestations

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Enzyme replacement therapy (ERT) is the standard of care for Gaucher disease (GD) types 1 and type 3

Dosage is individualized and based on disease severity and the presence of additional risk factors for bone disease progression

Bone manifestations require long-term treatment at higher dosage to achieve a therapeutic effect

Patients with significant skeletal involvement or other risk factors should receive high-dose therapy (60 U/kg/every 2 weeks)

Young patients should receive high-dose therapy to promote attainment of adequate peak bone mineral density during this critical period

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Tables 1 and 2) and thus may prevent serious skeletal complications such as bone collapse and fractures. Moreover, post-marketing pharmacosurveliance of more than 4,500 patients reveals that imiglucerase is associated with a stable and low rate of adverse events [46].

ERT improves the visceral aspects of GD in the first year, whereas skeletal involvement requires a longer treatment period [10]. Improvements in bone marrow infiltration are seen within the first 3 years of treatment with ERT [25], and better results are achieved at higher dosages [47]. A meta-analysis of clinical studies evaluated the effects of ERT on bone complications from GD, suggesting that the bone marrow fat fraction increases significantly following treatment and that 70% of adults with GD respond to treatment [48]. ERT increases the hyperintense T1-weighted MRI signal in bone marrow and significantly reduces BMB scores in patients with GD [28, 49].

On the other hand, normalization of BMD requires long-term treatment for up to 8 years, and there is a clear dose–response relationship [11, 50]. Appropriate dosage is based on disease severity and the risk of progression. Patients are considered to have high-risk disease if they have symptomatic skeletal involvement, significant visceral or hematological involvement, or, in the case of pediatric patients, if they exhibit growth failure [51]. The patient in Case 2 (Supplement) had a low BMD for his age (T-score −3.16) and had experienced a vertebral collapse. BMD did not respond to initial low-dose imiglucerase therapy; however, increasing the dosage to 60 U/kg every 2 weeks was associated with gradual normalization of BMD.

Data on 889 patients in the International Collaborative Gaucher Group (ICGG) registry revealed low BMD for chronological age among patients in all age groups, with the highest prevalence among adolescents [8]. ERT improved bone mass in all age groups, but the greatest effect was seen in younger subjects, emphasizing that a therapeutic window of opportunity exists and that high-dosage therapy may have the greatest effect in younger patients during the period when peak bone mineral density is accrued. Starting ERT sooner after diagnosis of GD is associated with better outcomes for avascular necrosis [14] and for bone outcomes in general [8]. However, ERT is also effective at stabilizing or slowing the progression of bone disease in adult patients who are diagnosed or treated late and may not have achieved peak bone density.

In patients with suboptimal bone responses to ERT, differential diagnosis should exclude other diseases that can mimic osteoporosis (e.g., osteomalacia, myelomatosis). It is very important to continue ERT at an optimal dosage in patients with poor or partial bone responses while evaluating concomitant conditions that may be driving bone mineral loss, such as hyperthyroidism, Cushing syndrome, hypogonadism, alcoholism, glucocorticoid therapy, or vitamin D deficiency.

Other Therapies

Patients who cannot receive treatment with ERT may benefit from substrate reduction therapy (SRT), which reduces the accumulation of glycosphingolipids by inhibiting the formation of their glucosylceramide precursors. Miglustat is a small molecule glucosylceramide synthase inhibitor licensed for use in adults with mild to moderate GD type 1. However, it is indicated as second line therapy due to its lower efficacy and tolerability [52, 53]. A second glucosylceramide synthase inhibitor (eliglustat) has shown statistically significant improvement in lumbar spine BMD in phase II trials [54, 55] and was recently approved in the US for use in adult patients with GD type 1.

Supportive Therapies to ERT for Treatment of Bone Manifestations in Gaucher Disease

Patients with bone mineral deficit may benefit from anti-osteoporotic drugs, in addition to specific therapy (ERT) for GD. The fracture risk assessment tool (FRAX®) from the World Health Organization quantifies the 10-year fracture risk from skeletal fragility due to primary osteoporosis and identifies a therapeutic threshold beyond which pharmacological treatment is indicated (http://www.shef.ac.uk/
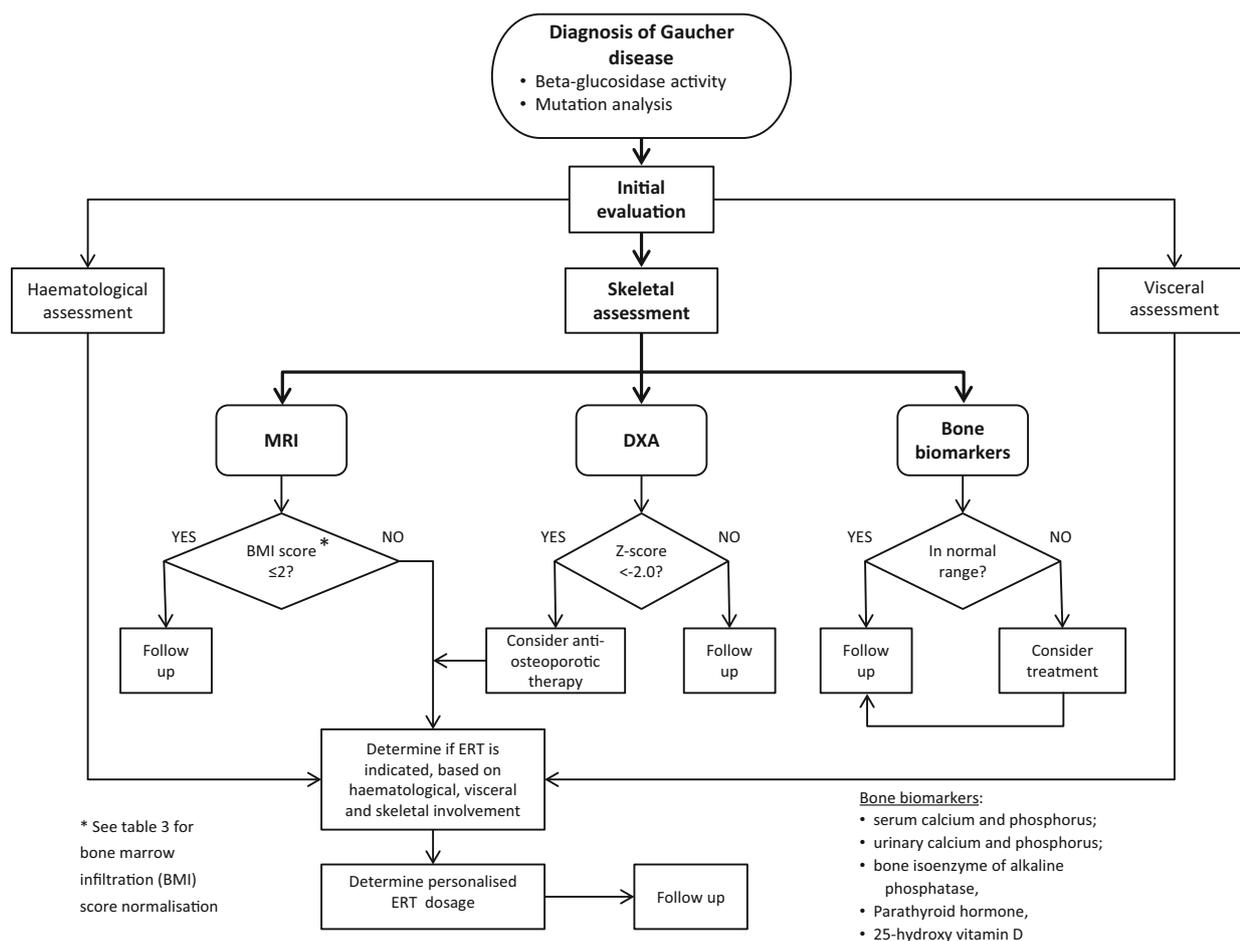
Fig. 1 Proposed algorithm for diagnosing and managing bone manifestations in patients with Gaucher disease. *BMI* Bone marrow infiltration, *DXA* dual energy X-ray absorptiometry, *ERT* enzyme replacement therapy, *MRI* magnetic resonance imaging

FRAX/index.aspx). In young subjects, a marked reduction in bone mass documented by DXA is an indication for anti-osteoporotic drugs, particularly bisphosphonates. Treatment with alendronate 40 mg/day provided a significant improvement in BMD at the lumbar spine in patients with GD [56]. Administration of bisphosphonates in GD is supported by guidelines from several scientific societies, though not as preventive therapy [57].

Algorithm for Diagnosis and Follow-Up of Bone Disease in Gaucher Disease Type 1

The flow charts in Figs. 1 and 2 show proposed algorithms for managing bone disease in GD type 1, based on the information and discussion in the preceding sections. Figure 1 depicts initial steps for diagnosis and treatment of patients, while Fig. 2 shows steps in monitoring for and follow-up of bone involvement.

CONCLUSION

The severity of skeletal involvement in type 1 GD is variable, but associated with significant pain, disability, and reduced QoL; thus, all patients should be monitored regularly for the onset and progression of skeletal pathology. DXA is the method of choice for measuring
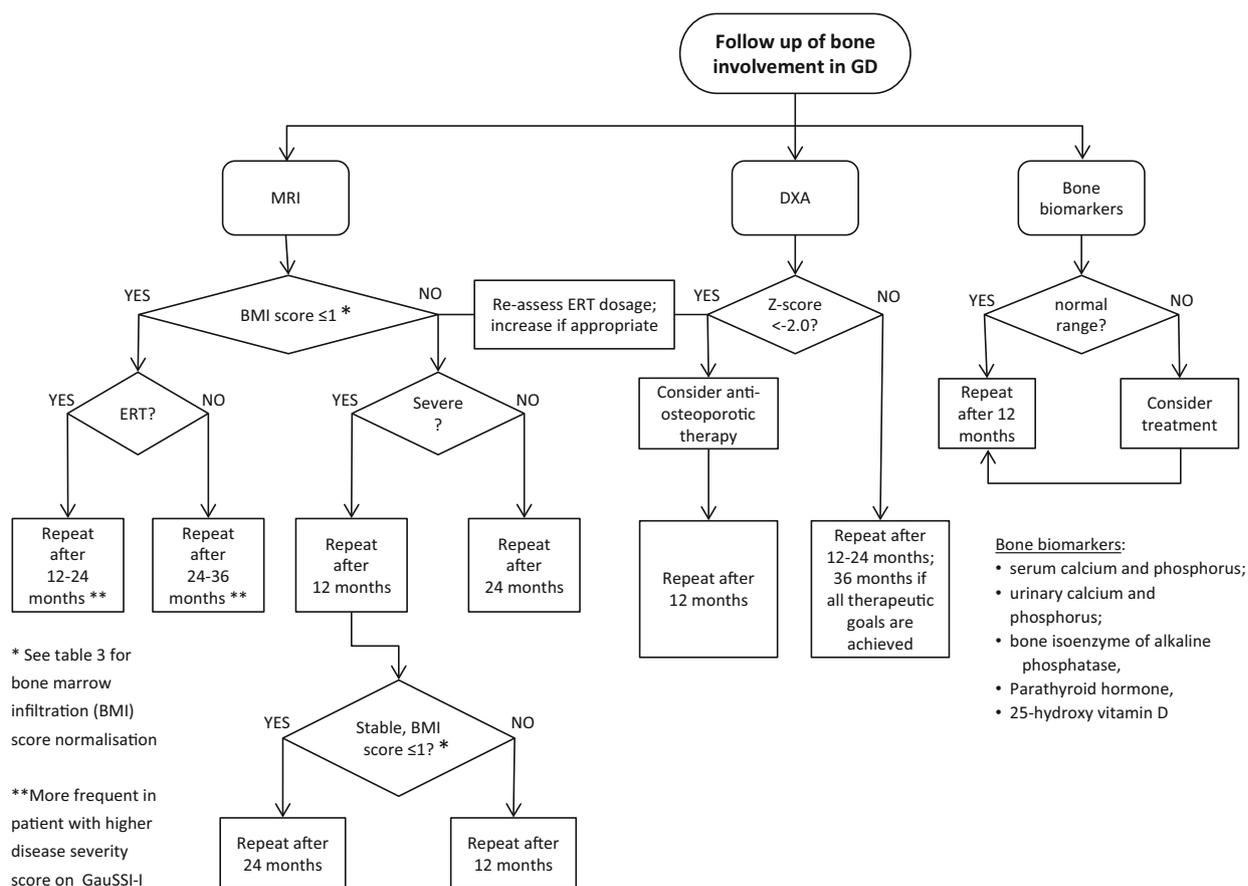
Fig. 2 Proposed algorithm for monitoring, and follow-up of bone involvement in patients with Gaucher disease. *BMI* Bone marrow infiltration, *DXA* dual energy X-ray absorptiometry, *ERT* enzyme replacement therapy, *GauSSI-I* Gaucher disease Severity Score Index-type I, *GD* Gaucher disease, *MRI* magnetic resonance imaging

BMD, whereas MRI is the method of choice for evaluating bone marrow infiltration. Correct performance and interpretation of these methods are paramount to obtaining clinically useful information.

ERT has changed the fate of patients with a diagnosis of GD, as demonstrated in numerous clinical studies. Continuous, long-term ERT should be considered for all patients with progressive skeletal involvement and those at risk of developing severe skeletal complications, including children with symptomatic GD. Early treatment at the appropriate individualized dosage is crucial for preventing irreversible skeletal damage. The dosage for individual patients is based on disease severity and response to therapy. Patients at high risk of skeletal disease should receive ERT at a dosage of 60 U/kg/2 weeks. Anti-osteoporotic therapy should be administered in addition to ERT when indicated.

Looking to the future, therapies combining ERT with SRT have the potential to provide further benefits [58]; however, a small 24-month controlled study did not show a significant benefit for combination therapy with imiglucerase plus miglustat, compared to either drug in monotherapy [59]. Combination therapies should continue to be investigated thoroughly as new agents emerge.

Skeletal manifestations of GD are not necessarily intractable, and patients who are diagnosed and treated early, before irreversible damage occurs, are spared from severe bone involvement. Registry data show that for most adults with late-diagnosed bone involvement, the onset of GD was in childhood. Thus, every effort must be made to monitor for skeletal involvement starting in pediatric patients.

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