

GAUCHER DISEASE TYPE 1 IN THE SKELETON: REVIEW OF LATIN AMERICA

DOENÇA DE GAUCHER TIPO 1 NO ESQUELETO: REVISÃO DA AMÉRICA LATINA

ENFERMEDAD DE GAUCHER TIPO 1 EN EL ESQUELETO: REVISIÓN DE AMÉRICA LATINA

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ABSTRACT

Gaucher disease (GD) is the most prevalent lysosomal storage disease, and is characterized by the accumulation of glucosylceramide and glucosylsphingosine in tissues throughout the body. With the advent of enzyme replacement therapy, the prognosis for patients with GD has dramatically improved. Still, the skeletal manifestations associated with GD respond slowly to enzyme replacement therapy and are the most significant contributor of disease related patient morbidity. This review of bone manifestations in GD presents the most recent theories on its pathophysiology, and gives a systematic review of studies with Latin American patients that report the frequency of bone manifestations and the effects of enzyme replacement therapy on their treatment. We conclude by emphasizing the importance of early identification and proper management at appropriate dosage levels of enzyme replacement therapy to reduce the morbidity caused by GD.

Keywords: Gaucher disease; Skeleton; Prevalence; Latin America.

RESUMO

A doença de Gaucher (DG) é a doença de depósito lisossômico mais prevalente, que se caracteriza pelo acúmulo de glicosilceramida e glucosil esfingosina em todos os tecidos do corpo. Com o advento da terapia de reposição de enzimas, o prognóstico dos pacientes com DG melhorou acentuadamente. Ainda assim, as manifestações esqueléticas associadas à DG respondem lentamente à terapia de reposição de enzimas e são as que contribuem de forma mais significativa para a morbidade do paciente. Esta revisão das manifestações ósseas da DG apresenta as mais recentes teorias sobre a sua fisiopatologia e uma revisão sistemática de estudos com pacientes latino-americanos que relataram a frequência das manifestações ósseas e os efeitos da terapia de reposição de enzimas sobre seu tratamento. Concluímos, destacando a importância da identificação precoce e do manejo adequado das doses apropriadas da terapia de reposição de enzimas para reduzir a morbidade causada pela DG.

Descritores: Doença de Gaucher; Esqueleto; Prevalência; América Latina.

RESUMEN

La enfermedad de Gaucher (EG) es la patología de depósito lisosomal más prevalente, que se caracteriza por la acumulación de glicosilceramida y glucosil esfingosina en todos los tejidos del cuerpo. Con el advenimiento de la terapia de reemplazo enzimático el pronóstico de los pacientes con EG ha mejorado notablemente. Sin embargo, las manifestaciones esqueléticas asociadas a la EG responden lentamente a la terapia de reemplazo enzimático y son las que contribuyen más significativamente a la morbilidad del paciente. Esta revisión de las manifestaciones óseas de la EG presenta las últimas teorías sobre la fisiopatología y una revisión sistemática de estudios de pacientes latinoamericanos que informaron la frecuencia de manifestaciones óseas y los efectos de la terapia de reemplazo enzimático en el tratamiento. Como conclusión, destacamos la importancia de la identificación temprana y del manejo adecuado de las dosis apropiadas de terapia de reemplazo enzimático para reducir la morbilidad causada por la EG.

Descriptores: Enfermedad de Gaucher; Esqueleto; Prevalencia; América Latina.

INTRODUCTION

Gaucher disease (GD) is an autosomal recessive disorder that affects around one in 850 individuals of Ashkenazi Jewish ancestry, and one in 40,000 individuals in non-Jewish populations. GD is caused by a rare inherited deficiency of the acid β -glucosidase enzyme, resulting in a continuum of phenotypes ranging from asymptomatic to severe childhood-onset.^{1,2} Broadly speaking, GD is classified into 3 different subtypes based on age of onset, clinical symptoms, and the presence and rate of progression of neurological symptoms. The most common

form of GD is type 1 (GD1)³ representing 95% of patients with the disease. In type 1, primary neurological disease is absent, differentiating it from types 2 and 3, which have varying degrees of central nervous system (CNS) involvement. Classical signs of GD1 disease generally include hepatosplenomegaly, thrombocytopenia, anemia and skeletal disease.³

GD1 is caused by pathogenic mutations in the *GBA* gene, which lead to a deficiency of the lysosomal enzyme, acid β -glucosidase, leading to storage of glucosylceramide and other glycolipids in various tissues, which cause damage to several organ systems.^{4,5} The widespread infiltration of these "Gaucher cells" in the tissues throughout the body,

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particularly in the liver, spleen, and bone marrow, but occasionally the lungs, skin and other organs,^{6,7} results in cytopenia, hepatosplenomegaly, and bone disease. Furthermore, there is evidence that individuals affected by GD are at a higher risk of developing autoimmune disorders,⁸⁻¹⁰ malignancies¹¹⁻¹³ and chronic inflammation.¹⁴ In addition, recent studies have found a connection between Parkinson's and GD that firmly suggests that the loss of the acid β -glucosidase function contributes to the pathogenesis of Parkinson's disease.¹⁵

While the underlying enzyme deficiency was identified in the 1970s, treatment for GD1 consisted only of palliative measures until 1990, such as splenectomy and hip replacement.¹⁶ It was not until 1991, with the advent of enzyme replacement therapy (ERT), alglucerase and more recently, imiglucerase (Sanofi Genzyme, MA, USA) that exogenous administration of the missing enzyme was brought to GD patients.¹⁷ The radical reduction of the liver and spleen were no less than an awe-inspiring triumph for translational medicine.¹⁸ With improved hemoglobin and platelet counts, ERT decisively changed the prognosis for patients with GD1. However, the skeletal manifestations of GD are slow to respond to ERT and are now believed to be linked to an underlying immunological dysfunction.¹⁸ In fact today, bone complications are the leading cause of morbidity in GD1 patients. The mechanism of action of the underlying pathophysiology of GD-related bone complications remains unclear, and is the subject of extensive research.¹⁹

The objectives of this review are four-fold: to (1) offer a brief overview of the pathophysiology of Gaucher-related bone disease; (2) to review the current diagnostic and imaging practices for clinical orthopedics; (3) to report the frequency of bone manifestations and present any studies that evaluate the effects of ERT on their progression, based on published studies in GD1 Latin American cohorts; and (4) to present the current frequency of bone manifestations reported in a Latin American cohort of the International Collaborative Gaucher Group (ICGG) Gaucher Registry (unpublished).

METHODOLOGY

Literature review

Several literature searches were made to retrieve all relevant articles for inclusion: 1) A PubMed search, using the search terms "Gaucher + bone" with a filter to include only those articles published in English and published in the last two years (9/31/2013 – 9/31/2015); 2) PubMed searches using the search terms "Gaucher + Latin America" and "Gaucher + [name of country]" to search for articles from the different countries in the Latin American region; and 3) Scielo electronic library (a repository for publications from the Latin American and Caribbean region) with the keyword "Gaucher".

The following inclusion criteria were used for selection of articles: published in English, Spanish or Portuguese; specifically related to Gaucher skeletal pathophysiology, prevalence, imaging or management; reported baseline prevalence data of skeletal manifestations in Latin American cohorts; reported bone manifestations of Latin American Gaucher patient cohorts at baseline or at two different time intervals of enzyme replacement or substrate reduction evaluation. Skeletal manifestations consisted of: bone pain, bone crisis, bone changes, Erlenmeyer flask deformity, osteopenia, marrow infiltration, infarction, avascular necrosis, fractures, lytic lesions, joint replacement and growth retardation. Articles excluded were those not related to GD skeletal manifestations, clinical trials, case reports or cohorts with less than five GD1 patients. A thorough bibliographic search was performed of articles that met the inclusion criteria. All articles that met the inclusion criteria were read, discussed and considered in the summary presented below.

Bone manifestations of Latin American Gaucher patients in the ICGG Gaucher Registry

Baseline bone manifestation data for all Latin American Gaucher patients as of May 2, 2014 were obtained from the ICGG Gaucher Registry. Treatment data were excluded, as the purpose of the request was for reported prevalence. All data presented were reviewed by the Gaucher Registry.

ICGG Gaucher Registry

Established in 1991, the ICGG Gaucher Registry (clinicaltrials.gov, NCT00358943) is the largest ongoing longitudinal international database that tracks demographic, biochemical and clinical outcome data from patients with GD. The Registry is governed by a collaborative group of international physicians who are experts in GD, with operational support provided by Sanofi Genzyme, and it is a strictly observational program. No experimental intervention is involved; patients in the Gaucher Registry undergo clinical assessments and receive care as determined by the patient's treating physician. Participation in the Registry is voluntary and open to all patients worldwide, irrespective of treatment status or treatment choice. Approximately 6,000 patients are currently enrolled in the Registry. Study had approval of the ethics committee (CAAE-20440713.2.1001.5440).

RESULTS

Figure 1 describes the search results. A total of 256 abstracts were reviewed, from which 31 articles were selected to be read in their entirety, along with 52 additional articles from an extensive bibliographic search. A total of 68 articles were referenced: 14 articles for the systematic review and 54 that were used in the integrative summary of best practices.

Pathophysiology of skeletal manifestations

During one's lifetime, the bone is constantly remodeling itself through a carefully balanced process in which old bone areas are removed by osteoclasts and replaced with new bone tissue from osteoblasts.^{20,21} To maintain the delicate balance in the bone environment, the final phase of osteoblast differentiation is believed to be carefully controlled²² as osteoblasts are responsible for stimulating osteoclast differentiation.²³ Studies in osteoimmunology describe this process as a complex interaction between bone cell development and immune cells, and point to activated T-cells as key players in this involvement, given their production of a number of inflammatory cytokines²⁴ either directly or indirectly regulating the cells involved in the bone turnover balance – shifting in either direction, bone reabsorption or bone generation.

The infiltration of Gaucher cells into the bone marrow, along with the increase of pro- and anti-inflammatory cells in GD – which are highly variable but likely result in a chronic pro-inflammatory state – results in an overall immune dysfunction²⁰ and a resulting dysfunction of the delicate bone remodeling balance. While the mechanism of the remodeling dysfunction is not completely understood, studies point to an osteoclast-osteoblast uncoupling. It remains uncertain as to whether the dysfunction lies with the osteoblasts or osteoclasts, or whether it is both sides of the bone turnover balance that are affected. Nevertheless, it remains an area of fascinating research. Overall, we can substantiate the fact that there is either no change, or a decrease in osteoblast proliferation, in conjunction with either no change or an increase in osteoclast proliferation.^{20,25-27}

Prevalence of bone manifestations in Latin American GD1 patients ICGG Gaucher Registry (current)

A total of 926 Latin American patients were identified with GD in the ICGG Gaucher Registry as of May 02, 2014. Of the 917 patients with a reported disease type, 95% were physician designated as GD1 patients and 5% as GD2/GD3. The vast majority of these patients came from Brazil (64%). Slightly more females than males were registered (59% versus 41%, respectively); 81% had not undergone a splenectomy. The mean age at diagnosis was 16.5 years (median = 10.8, 25th percentile = 5.1, 75th percentile = 24.6 years). Among the 845 imiglucerase-treated patients in this study population, the average age at the start of treatment was 20.7 years, with ages ranging from 0.6 to 80.4 years.

Our study evaluated the baseline measures of the 845 imiglucerase-treated patients (91%), excluding the 81 never treated patients (9%). Baseline for the assessment of the bone manifestations is defined as the data point closest to the initiation date of imiglucerase treatment

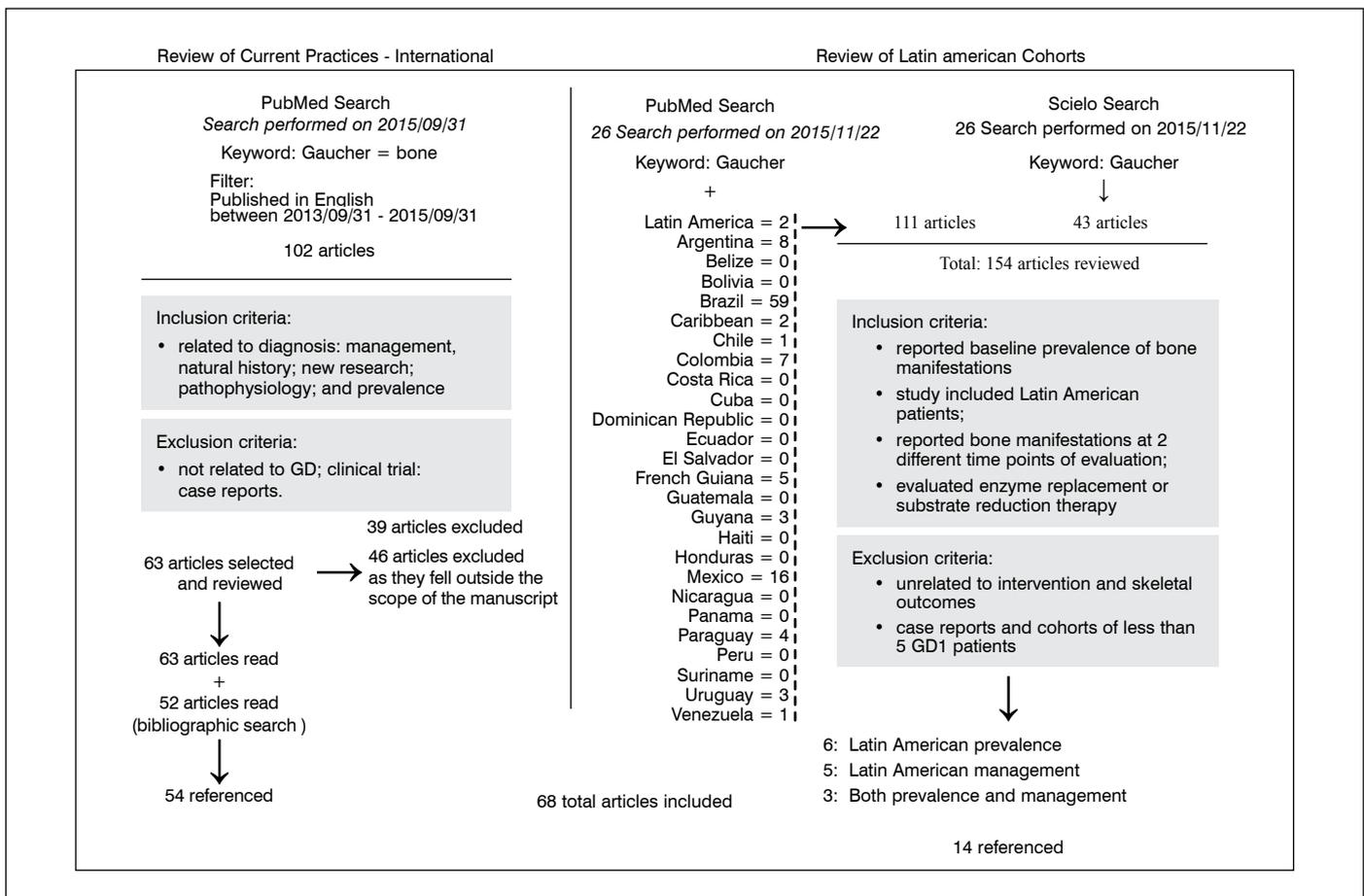


Figure 1. Flowchart describing the search results for GD.

using a window of no more than -2 years to +6 weeks from the start of treatment. Indicators of bone disease reported for our Latin American cohort (N=845) are limited. Only bone crises and bone pain are reported for more than 50% of the cohort. Other skeletal manifestations such as bone marrow infiltration, avascular necrosis, infarction, lytic lesions, Erlenmeyer flask deformity and fractures are reported in less than 25% of the study population, and should be cautiously interpreted. Table 1 presents these data along with the results of other Latin American cohorts retrieved in the literature search.

Dual energy X-ray absorptiometry (DXA) Z-scores for the lumbar vertebrae and the femur was reported from only 6% (50/845) and 2% (14/845) of the cohort, respectively. DXA Z-scores were reported categorically (mild or none = > -1 ; moderate = > -2.5 to ≤ -1 ; or severe = ≤ -2.5). Moderate or severe Z-scores of BMD of the lumbar vertebrae were reported in 44% and 24% of the patients and of the femur in 29% and 7%, respectively.

Review of the literature

We found a total of 9 published articles reporting prevalence of bone manifestations in Latin American GD1 patients at baseline.²⁸⁻³⁶ The prevalence values reported in these articles are presented in Table 1, with registry and non-registry cohorts reported separately.

Bone pain and bone crises

Bone pain, whether acute or chronic, is commonly experienced amongst patients with GD, with varying degrees of severity. This subjective symptom shows similarities to osteoarthritis, with pain often occurring with temperature and weather changes.³⁷ The most severe manifestation of bone pain is an acute episode of excruciating skeletal pain, referred to as a *bone crisis*. Less frequent but far more severe than bone pain alone, bone crises typically begin with regional dull, aching pains that continue to increase over a period of several days,

resulting in intense pain that may last for 7-10 days often followed by weeks of dull aches.¹⁹ These crises are often accompanied by fever, elevated white blood count, tenderness and swelling, and often require hospitalization or the use of potent analgesic drugs for pain management.³⁸ Acute bone crises can be confirmed through magnetic resonance imaging (MRI) showing localized edema of the soft tissues and bone marrow: an increased signal on T1-weighted images at the site of the crisis is suggestive of hemorrhage.³⁹ Bone crises typically occur in the long bones but may also occur in other bones such as the skull or pelvis. Bone crises should be differentially diagnosed from osteomyelitis through a negative bacterial blood culture.

Radiologic bone manifestations

The pathophysiological mechanisms of GD manifest themselves through a variety of bone complications, often in the presence of visceral disease or bone pain.¹⁶ Therefore, it is essential to conduct a thorough assessment of the skeleton in all patients newly diagnosed with GD, even asymptomatic patients, as bone complications can become irreversible if left untreated, and studies have shown that asymptomatic patients with GD can show radiological findings of skeletal manifestations.⁴⁰ The most common radiological findings are described below:

- Bone Marrow infiltration (BMI)** occurs when normal marrow cells are replaced with Gaucher cells⁴¹ causing ischemia and as a result, edema and pain (Figure 2A, B and C). Those bones adjacent to infiltration may exhibit cortical thinning, osteopenia and deformity. The focal areas of infiltration vary across individuals; however, it is suggested that marrow infiltration extends from the axial to the appendicular skeleton.⁴¹
- Osteonecrosis** (also known as avascular necrosis) is bone death reported to be a result of ischemia due to chronic infarction (Figure 2D and E). Affecting predominantly the femoral head, proximal humerus and vertebral bodies, osteonecrosis may also result in

Table 1. Reported prevalence of bone manifestations in Latin American Cohorts.

Country	Study	Ages*	Range/median	Gender**	Splenectomy ***	Bone pain	Bone crisis	Bone changes	Erlenmeyer flask deformity	Osteopenia	Marrow infiltration	Infarction	Avascular necrosis	Fractures	Lytic lesions	Joint replacement	Growth retardation
Number of patients with bone manifestation/Total patients in cohort																	
ICGG Registry cohorts																	
Brazil	Sobreira, 2007 (28)	A	-	MF	NS	45/78	14/87	-	26/53	-	-	-	5/53	4/53	9/53	-	-
			% in sample			0	58	16	49				9	8	17		
Brazil	Sobreira, 2008 (29)	CA	1-55 yr 11.8	MF	S	44/90	-	-	-	-	-	-	-	-	-	-	-
			% in sample			24	49										
Latin America ¹	Drelichman, 2012 (31)	CA	-	MF	S	228/475	60/462	9/39 [#]	119/190	128/183	127/151	52/159	40/165	14/129	55/163	-	-
			% in sample			7	48	13	23	63	70	84	24	11	34		
Latin America ²	Current study	CA	-	MF	S	204/448	51/436	-	111/149	-	105/130	42/135	39/141	11/118	48/151	-	-
			% in sample			21	46	12	74		81	31	28	9	32		
All ages, splenectomy status, gender						46-58%	12-16%	23%	49-74%	70%	81-84%	31-33%	9-28%	8-11%	17-34%	-	-
Non Registry cohorts																	
	Mendonça, 2001 (32)	CA	4-62 yr 28.9	MF	NS	-	-	-	30/32	32/32	-	-	9/32 ^{##}	3/32	9/32	13/32	-
			% in sample			0			94	100			28	9	28	40	
Brazil			Subset	M	NS	-	-	-	13/14	14/14	-	-	3/14	1/14	7/14	7/14	-
			% in sample			0			93	100			21	7	50	50	
			Subset	F	NS	-	-	-	17/18	18/18	-	-	3/18	2/18	2/18	6/18	-
			% in sample			0			94	100			17	11	11	33	
Brazil	Oliveira, 2002 (36) ³	C	1-10 yr	MF	S	5/13	-	5/13	-	-	-	-	5/13	5/13	-	-	-
			% in sample			38	38	38					38	38			
Argentina	Drelichman, 2007 (30)	C	1-12 yr	MF	NS	3/5	-	-	-	3/5	-	-	-	-	-	-	4/5
			% in sample			0	60			60							80
Brazil	Mota, 2007 (33)	C	3-18 yr	MF	S	-	1/18	1/18	1/18	1/18	6/18	1/18	-	-	7/18	-	-
			% in sample			0.6	6	6	6	6	33	6			39		
Brazil	Ferreira, 2008 ⁴ (34)	CA	-	MF	NS	-	-	-	2/10	4/10	1/10	1/10	3/10	1/10	-	-	-
			% in sample			0			20	40	10	10	30	10			
Brazil	Oi, 2013 ⁵ (35)	A	-	MF	NS	-	-	-	2/5	4/6	-	-	1/5	1/5	1/5	-	-
			% in sample			0			40	60			20	20	20		
All ages, splenectomy status, gender						38-60%	6%	6-38%	6-94%	6-100%	10-33%	6-10%	17-38%	7-38%	11-39%	33-50%	80%

* Children and adult (CA); children (C), adult (A); ** Male and female (MF); male (M); female (F); *** (NS) Non-splenectomized patient only; (S) cohort includes splenectomized patients; not reported (-); # Reported bone changes are reported lumbar vertebrae DXA Z-scores categorized as: no or mild (>-1) 15/39; moderate (>-2.5 a ≤ -1) 15/39; severe (≤ -2.5) 9/39. Data presented in Table 1 reports only those severely affected; ## Both femur and humerus AVN were reported, though only data reporting the femur AVN was included in the above table. This decision was made based upon the manuscript explanation that all of those who had avascular necrosis in the humerus also had it in the femur, but not vice versa. Full reporting in the manuscript was as follows: (9/32f, 2/32h); male (6/14f; 1/14h); female (3/18f; 1/18h); f=femur and h=humeral; AVN = avascular necrosis; Δ The current study population comes from a larger cohort of 926 patients including those "never-treated". The entire cohort of 926 patients consisted of 19% (176 patients) who had undergone a splenectomy. Unfortunately, we do not have the % of patients with a splenectomy in our subset of 845 patients, though it would be 176 patients or less. While we have listed the maximum possible percentage of splenectomized patients in our sample, it is likely much less than this percentage; 1 Did not report the countries enrolled in the study; 2 "Baseline" is defined as the data point closest to the initiation of imiglucerase treatment using a window of no more than -2 years to +6 weeks (inclusive) from the start of treatment for all parameters. Baseline data presents 845 Latin American patients with all disease types that went on to receive treatment with imiglucerase as of May 2, 2014. It should be noted that these 845 patients are part of the larger Latin American ICGG Gaucher Registry patient cohort of 926 patients - of which 917 had a disease type specified by physicians with 95% reported as GD1 and 5% as GD2/GD3. The 926 Latin American patients include both imiglucerase-treated (845) and never-treated (81) patients as of May 2, 2014. Distribution of Latin American imiglucerase-treated patients at baseline, by country, is as follows: Argentina (n=115; 13.6%), Bolivia (n=1; 0.1%), Brazil (n=540; 63.9%), Chile (n=20; 2.4%), Colombia (n=77; 9.1%), Costa Rica (n=2; 0.2%), Dominican Republic (n=1; 0.1%), Ecuador (n=2; 0.2%), Guatemala (n=2; 0.2%), Mexico (n=11; 1.3%), Panama (n=1; 0.1%), Paraguay (n=2; 0.2%), Peru (n=6; 0.7%), Suriname (n=1; 0.1%), Uruguay (n=1; 0.1%) and Venezuela (n=63; 7.5%); 3 Of the splenectomized patients in this cohort 4/13 (31%) had a total splenectomy and 1/13 (8%) had undergone a partial splenectomy; 4 This cohort contains both GD1 [8/10 -80%] and GD2 [2/10 -20%] patients; 5 All members of the same family.

fracture and joint collapse.^{40,42-44} Not only is osteonecrosis irreversible once the necrotic process starts, it is the most clinically significant and disabling skeletal manifestation in GD,⁴⁵ often presenting as bone crises, and is one of the most important reasons for early treatment. The Ficat staging system and Mitchell classification are useful for monitoring osteonecrosis through radiography and MRI, respectively.^{46,47}

- **Bone mineral density (BMD)** measures minerals i.e. calcium in the bones and is the best measure to quantify weakening of the bone. It is measured with DXA and is reported as Z- and T- scores.⁴⁸ A Z-score of less than -2.0 indicates a "BMD lower than the expected chronological age" in premenopausal women, men <50 years and the pediatric population >5 years. For postmenopausal women and men >50 years, a T-score of between -1.0 and -2.5 is classified as *osteopenia*; and a T-score <-2.5 is considered as *osteoporotic*.⁴⁹ (Figure 2)
- **Lytic lesions**, or "holes" that weaken the bone may occur, causing pain and increasing the risk of fractures in these patients.
- **"Erlenmeyer flask" deformity** is the result of impaired remodeling of the metaphyseal region of the tubular bones, which leads to flaring of the distal lateral aspects of the femur and proximal tibia where the proximal femur narrows relative to the distal femur.⁴⁸ This expansion of the medullary cavity and the thinning of the

load-bearing cortices of the long bones weakens the bone structure, predisposing it to fractures.⁵⁰

- **Fractures** are associated with considerable pain and disability, particularly when the spinal column is involved.

Growth

Children affected with GD may have normal growth during the first 2 years of life, after which the growth rate often slows, resulting in severe growth impairment in many GD patients.¹⁸ Growth impairment in GD patients was examined in a study of the ICGG Gaucher Registry Global cohort,⁵¹ which showed that treatment with imiglucerase (ERT) could improve height z-scores significantly. In our literature search of Latin American cohorts, we found only a single study that examined growth in 5 Latin American children with GD. This study reported that 4 out of the 5 were below the 5th percentile for growth for their age and sex.³⁰ International studies have supported that treatment with ERT can normalize growth for children affected with GD.⁵²

Imaging methods for assessing bone damage Radiography (X-ray)

An initial X-ray examination of the femora, spine or other symptomatic site can not only detect fractures, but may also reveal skeletal lesions, cortical bone thinning and Erlenmeyer flask deformation, and can lead to the identification of asymptomatic patients with GD. X-ray

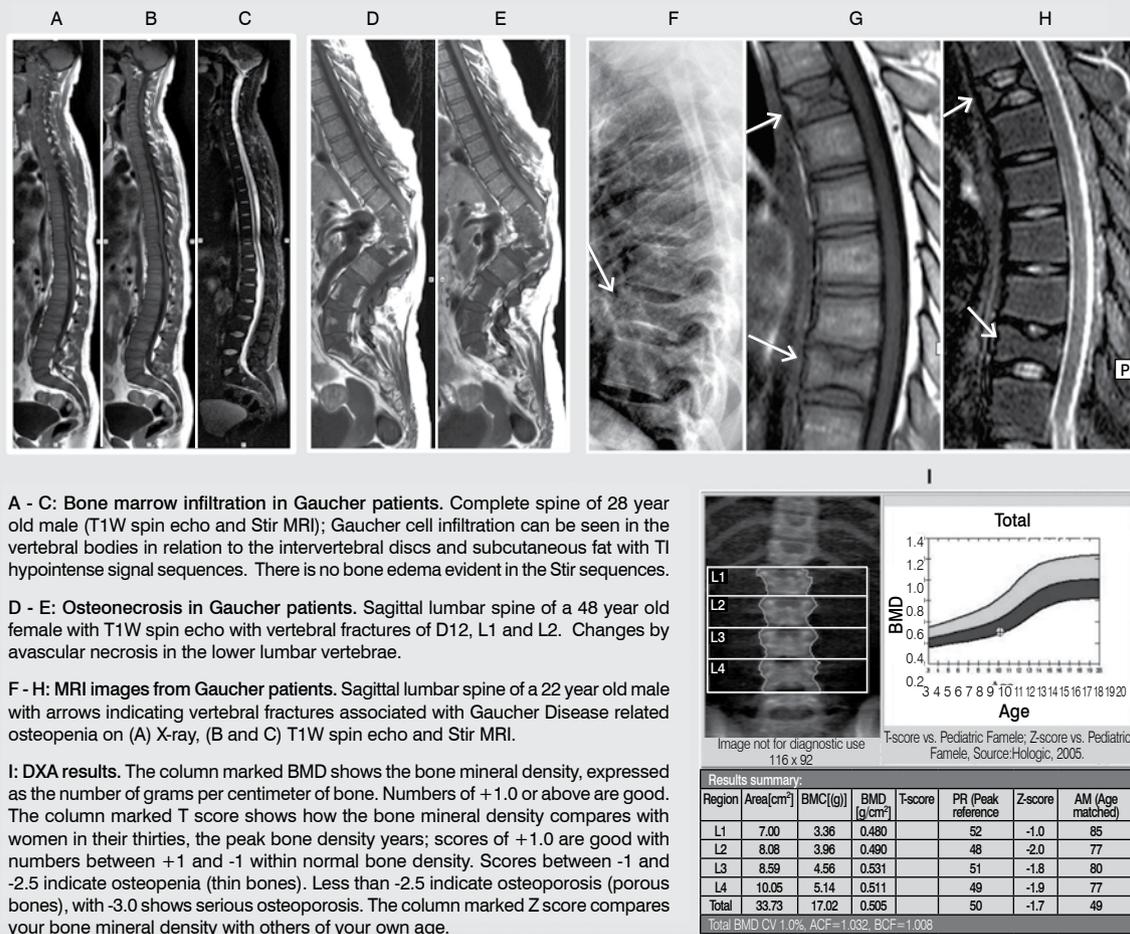


Figure 2. Radiological manifestations found in GD patients.

can also be useful in characterizing osteonecrosis of the proximal femur and osteosclerotic areas (using a classification system such as that Steinburg or University of Pennsylvania).⁵³

Vertebral fracture assessment (VFA) can be performed through lateral spine radiography in conjunction with the Genant semi-quantitative method.⁵⁴ This method is considered the gold-standard for VFA. The cortical edges and endplates of these images are well-defined, resulting in less image "noise" and higher spatial resolution, which allows for more of the vertebrae to be evaluated. The method developed by Schousboe et al.⁵⁵ considers the shape of the vertebrae and the approximate loss of vertebrae height based on fixed values of loss (0.60, 0.75 and 0.80). Alternative methods, such as DXA, are slightly less precise, but offer a substantial reduction in cost and exposure to radiation, as the analysis can be performed alongside measurement of bone density with DXA requiring only 3-40 microsieverts, whereas lateral thoracic and lumbar spine radiographs require close to 600 or more microsieverts.⁵⁵

Magnetic resonance imaging

One of the most sensitive methods for monitoring GD bone pathology is MRI, due to its ability to assess BMI in adult patients.⁴⁹ The displacement of fatty marrow by Gaucher cells can be identified in less intense signal in hyperintense T1 and intermediate-to-hyperintense T2-weighted signals.⁴⁹ Assessing BMI in pediatric patients, however, is not feasible due to the lack of standardized methods that account for age-related conversion of hematopoietic bone marrow to fatty bone marrow in children.⁴⁹ Active bone marrow events and osteonecrosis can be detected by increased signal intensity in both T1- and T2-weighted images, but as these may be obscured by Gaucher cell infiltration, hyperintense signal in short

tau inversion recovery (STIR) is often used. (Figure 2F, G and H)

Improvements in this infiltration as a result of treatment with ERT can be monitored as marrow fat content increasing and normalizing the signal intensity. In efforts to better quantify the qualitative MRI, both quantitative and semi-quantitative methods have been developed. Quantitative chemical shift imaging (QCSI)⁵⁶, for example, is an MRI method that measures fat content using differences in the resonant frequencies of fat and water in bone marrow. This technique is time consuming and prone to errors, mainly due to the lack of availability of QCSI and the fact that it requires specialized technicians to perform, therefore clinicians have more readily adopted the semi-quantitative methods that have been developed (6 in total). The most commonly used semi-quantitative method is the bone marrow burden (BMB) score, which was developed using signal intensity changes at sites of involvement in the peripheral skeleton to generate a single score that reflects bone disease severity (both axial and peripheral bone marrow in GD patients).⁵⁷

Based on the most recent recommendations by Giuffrida et al.⁴⁹ MRIs should be conducted at baseline and followed up every year if the normalized score is >1, every 2 years if the normalized score is ≤1, and every 3 years in stable patients with good metabolic control and consistently normalized scores ≤1.

Dual energy X-ray absorptiometry

DXA is considered the gold standard for quantitative assessment of bone mineral status in adults and children over the age of 5.⁴⁹ Important parameters to investigate are: 1) bone mineral weight (g) and bone area (cm²) so that BMD (g/cm²) can be calculated for the lumbar spine (L1-L4); 2) total body less head (TBLH); and 3) in adult patients, proximal femur (total hip and femoral neck).

Protocols should adhere to the International Society for Clinical Densitometry (ISCD) 2013 position document⁵⁸ as there are several causes that can lead to both under- and overestimation of BMD due to the 2-dimensional nature of DXA and the influence of bone size, skeletal maturity and pubertal stage.⁴⁹

The DXA for adults and children is interpreted using the Z-score, with scores below -2.0 indicating a reduced BMD. (Figure 2) For post-menopausal women and men of the age of 50 and older, the T-score is interpreted using the World Health Organization (WHO) classification for osteopenia/osteoporosis. Ideally, DXA should be performed at baseline and annually in untreated, asymptomatic patients, and in patients who have not reached therapeutic goals on ERT. In patients who have met their therapeutic goals and who have no intercurrent conditions associated with BMD loss, follow-up every 3 years is adequate.⁴⁹

Management/treatment

Therapeutic goals for GD were established in 2003,⁵⁹ with the pediatric goals updated and revised in 2013.⁶⁰ Early diagnosis is strongly suggested where there is clinical suspicion requiring laboratory or genetic testing to confirm diagnosis of GD. Treatment goals include specific targets for liver and spleen size, hemoglobin, platelet count, as well as skeletal manifestations of bone pain, crises, osteonecrosis and BMD. As the standard of care for GD1, ERT dramatically improves the visceral aspects of the disease. While ERT has been shown to improve bone outcomes, the response of the immune system dysfunction is

slower and more difficult to quantify, and skeletal complications continue to be the main cause of morbidity in these patients. Early treatment is key, especially in children, in efforts to attain peak bone mass, but in adult patients too, who may have been diagnosed or treated late in life and never achieved peak bone mass, ERT can slow down the disease or even stop the progression of skeletal manifestations. Improvements in BMI are usually seen within the first 3 years of treatment.⁶¹

In our review of studies including Latin American patients undergoing intervention for Gaucher disease, we summarized the studies that had two time points at which patients underwent an intervention, and examined the outcome on skeletal manifestations. These studies^{29,30,33,62-66} showed similar outcomes to the international literature and consensus⁵⁹ providing evidence that treatment, especially early intervention, improves skeletal outcomes. (Table 2)

DISCUSSION

We have summarized the key points of our review in Box 1, highlighting the underlying pathology, clinically suspect symptoms, diagnosis, manifestations, and imaging practices. Studies from the ICGG Gaucher Registry and other published cohorts are invaluable for the advancement of our understanding of GD. Adding to this literature base, and the early identification of GD1 patients, should be the goals for the Latin American region.

ERT is still relatively new - only now are we seeing the adults who

Table 2. Summary of Latin American Studies with treatment intervention or stop treatment lapse at two different time points.

Study	Country	Sample	Study Objective	Affects on Bone Manifestations	Key point
Mota, 2007 (33)	Brazil	18 children	Patients were followed for up to 10 years (mean follow-up, 4 years and 4 months \pm 3 years and 3 months). Bone changes were evaluated by plain radiographs in all patients.	Clinical and radiological improvement was noted in 13 (72%) of 18 patients; bone lesions worsened in 5 (28%) of 18 patients. Final ERT dose was statistically different between those who improved versus those who worsened (55 ± 10 U/kg vs. 29 ± 2 U/kg; $P < 0.03$).	Importance of ERT dose
Drelichman, 2007 (31)	Argentina	5 children	5 children had at least 1 year of ERT but therapy was discontinued for 1 to 3 years. These features were measured at baseline (immediately before initiating ERT), when ERT was withdrawn, when ERT was resumed, and at least 11 months after resuming ERT.	Before ERT was interrupted – no radiological skeletal manifestations were present. 4 of the children interrupted on ERT had serious bone manifestations requiring hospitalization, immobilization, and analgesics; after 9-11 months of ERT re-initiated the radiological manifestations continued to persist. Suggesting 4 out of the 5 children whose ERT was interrupted had sustained irreversible skeletal damage and resulting disability.	Implies prevention of bone problems with ERT in children and importance of continued use
Parisi, 2008 (62)	Argentina	9 adults	Evaluated bone composition in GD1 patients receiving imiglucerase in a mean dose of 53 ± 13 IU/kg/2weeks, during 4.9 ± 3.9 years and compared with 145 sex and age matched healthy individuals	GD1 patients receiving the lower dose of ERT (<60 IU/kg/2weeks) presented lower BMD values than those receiving the higher dose (≥ 60 IU/kg/2weeks) (0.968 ± 0.032 vs. 1.088 ± 0.061 g/m ² , respectively, $p < 0.001$).	Importance of ERT dose
Sobreira, 2008 (29)	Brazil	41 children 71 patients	Evaluated individuals with GD1 at baseline and after 24 months of mean dosage of imiglucerase 35 UI/kg/2 weeks	From baseline to 18 months, the frequency in short stature was significantly reduced. Incidence of bone pain also progressively reduced from baseline to 18 months, reaching statistical significance as early as 6 months.	ERT improved growth and bone pain
Lukina, 2014 (63)	Multi-centered includes Argentina and Mexico	19 adults	Phase II Trial of Eliglustat – a substrate reduction therapy over 4 years in treatment naïve GD1 (18-56 yo)	Mean bone mineral density T-score for the lumbar spine increased by 0.8 (60%) (baseline: -1.6 ± 1.1). Femur dark marrow, a reflection of Gaucher cell infiltration into bone marrow was reduced or stable in 17/18 patients. There were no bone crises.	Improved lumbar spine T-score and BMI
Hughes, 2015 (64)	Multi-centered includes Argentina and Paraguay	57 patients	Long-term data from velaglucerase alfa phase III clinical trial in a single extension study (aged 3-62) Measures reported over 24 months (extension plus Phase 3)	Lumbar spine BMD Z-scores in adults improved by 24 months, no difference in mean Z-score changes in the femoral neck likely because most patients ($>64\%$) at baseline were no more than 1 SD below peak bone density at the femoral neck, which is considered normal.	Improved on lumbar spine z-score measure, but not on others
Mistry, 2015 (65)	Multi-centered includes Colombia and Mexico	40 patients	Eliglustat (substrate reduction)-Phase 3, randomized, double-blind, placebo-controlled trial conducted at 18 sites in 12 countries.	Eliglustat treatment resulted in a statistically significant improvement in mean total BMB score and there was no change in the placebo treatment group, $P = 0.002$. Other markers of bone disease, including BMD, showed no significant change.	Improved BMB but not BMD
Cox, 2015 (66)	Multi-centered includes Argentina and Brazil	160 patients	Phase 3, randomized, open label, non-inferiority trial of 106 Eliglustat versus 54 imiglucerase; Average age 37.6 yrs (14.2)* and 37.5 yrs (14.9)*	Mean bone mineral density was in the normal range and maintained; mean bone marrow burden scores showed moderate infiltration of haemopoietic marrow and were also maintained	BMD and BMB were within the normal range and were maintained

* - Mean (SD)

started treatment in childhood. Experts agree that there is an optimal time window to start treatment, if maximum benefits are to be obtained. Notably, one of the most important pediatric milestones in GD is attaining maximum peak bone mass in order to significantly reduce the morbidity associated with skeletal manifestations in adulthood.⁶⁷

The idea that early treatment changes the natural course of the disease is nothing new, and is accepted almost across the board by researchers and clinicians working with lysosomal storage disorders for which ERT is available. As GD is so phenotypically variable, what

an individuals' disease would actually be without ERT treatment is unknown, and cannot be quantified. This concept was reiterated in a recent Cochrane meta-analysis that ascribes to the effectiveness of ERT, but attests to the difficulty in quantifying its long-term impact due to the disease-modifying nature of ERT in a life-long disorder.⁶⁸ However, even when the disease is identified and/or treated late, treatment can still bring valuable benefits.

All the studies cited in this review have the same source limitations. As an observational database, the ICGG Gaucher Registry has some inherent limitations in that it is voluntary and depends on the collaboration of the physicians who manage GD patients. For example, phenotypes can vary widely with the presence or absence of manifestations, which are highly dependent on the time at which the patient was examined (e.g. a 2 year old would probably not present with the same manifestations as a 60 year old with severe disease). Also, the non-registry cohorts from the Latin American region have a limited number of patients, as is often the case with rare diseases, and may not be representative of all GD1 patients. Another limitation in our study is that it is many of the patients reported in one study may also be included in the other cohorts we presented, especially in studies from the ICGG Gaucher Registry. Nevertheless, in presenting these data, we have attempted to give a general idea of the frequency of skeletal manifestations in GD1 patients across the region.

With over 300 mutations, researchers continue their efforts to link the GD genotype and phenotype. But as the field of genetics advances, we are becoming even more mindful of the complexity, due to modifier genes, gene polymorphisms and other factors influencing the rampant phenotypic variability.²¹ Despite these complexities, the field is advancing, and will usher in even earlier identification, offering hope in making truly impactful management of the manifestations of GD.

CONCLUSION

Unlike more common disorders, rare diseases have become a controversial health system issue. However, the evidence for therapeutic intervention for GD has won over skeptics, demonstrating undeniable disease modifying effects, substantial returns in quality of life, and a reduction in disease morbidity and mortality. Rarely do we have an opportunity in medicine to alter the outcome of a patient as substantially as is the case with ERT for GD patients. Research continues to advance our understanding of this rare disease and has led to truly life-changing interventions for these patients. Awareness of these disorders is pivotal for those clinicians who are at the front line with the patients, so that they can provide the optimal individualized therapy and ultimately, offer hope for these patients. It is our humble goal that this review will contribute to this objective.

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Box 1. Summary of key points for Gaucher disease type 1.

Associated Gene Pathological mutation in the <i>GBA</i> gene on chromosome 1q with 11 exons (GenBank No. J03059).	
Underlying pathophysiology Deficiency in the acid β -glucosidase enzyme (EC.3.2.1.45) causes an accumulation of substrates glucosylceramide and glucosylsphingosine in macrophage lysosomes	
Clinical suspicion* Hepatosplenomegaly Thrombocytopenia +/- anemia Characteristic bone lesions	
Diagnostic tests Gold standard for GD diagnosis: acid β -glucosidase enzyme activity - Measured in peripheral blood leukocytes with a fluorometric assay when GD is suspected Molecular genetic testing offers information on prognosis and facilitates family screening - Full sequencing of <i>GBA</i> will identify the 2 causative mutations in 99% of GD patients	
Clinical manifestations Hepatosplenomegaly Thrombocytopenia Anemia Skeletal disease including - Bone pain - Bone crises - Bone changes - Erlenmeyer flask deformity - Osteopenia - Marrow infiltration - Infarction - Avascular necrosis - Fractures	Associated risks Slower resolution of infections Autoimmune disorders Malignancies Parkinson's disease
Imaging X-ray may be used as an initial exam to identify fractures, skeletal lesions, cortical bone thinning and Erlenmeyer flask deformation MRI is very useful to identify bone marrow infiltration for diagnosis and follow-up evaluations of patients with GD T1-weighted MR images can measure the marrow fat; 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. T2-weighted MRI and short-tau inversion recovery (STIR) can evaluate avascular osteonecrosis Semi-quantitative method can be attained with BMB score and MRI DXA is the gold standard quantitative method and measures bone mineral density with the use of Z and T scores.	

* greater suspicion in those of Ashkenazi Jewish ancestry

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