Osteoarticular manifestations of Gaucher disease in adults: pathophysiology and treatment

Rose-Marie Javier¹, Éric Hachulla²

1. Service de rhumatologie, Hôpital de Hautepierre, Avenue Molière, Strasbourg (67)
2. Service de médecine interne, Hôpital Claude Huriez, Centre national de référence maladies métaboliques rares, Lille (59)

Correspondence:
Rose-Marie Javier, Service de rhumatologie, Hôpital de Hautepierre, Avenue Molière, 67098 Strasbourg.
Rose-marie.javier@chru-strasbourg.fr

Key points

Gaucher disease frequently entails severe and potentially disabling osteoarticular manifestations.
Ischemic phenomena cause the most serious complications and lead to irreversible lesions. Aseptic osteonecrosis of the hip is the most disabling complication; it causes intense early bone pain and sometimes joint collapse and secondary osteoarthritis in young adults.
Localized or systemic bone fragility explains osteopenia, osteoporosis, and fractures (vertebral collapse with irreversible kyphosis causing chronic morbidity).
Although no double-blinded randomized studies have assessed the bone effects of enzyme replacement therapy, it has been shown to be effective in reducing bone pain in about half of all treatment-naive patients within 1 to 2 years and in improving bone mineral density after 3 years. In open-label trials, substrate reduction therapy (miglustat) reduced both bone pain and bone marrow infiltration.
Specific treatment for bone fragility, with bisphosphonates for example, should be considered after rigorous individualized evaluation and assessment of other risk factors.

To cite the present paper, use exclusively the following reference:
Free full text in english on www.masson.fr/revues/pm
Gaucher disease, first described by Philippe Charles Ernest Gaucher in 1882, is the most common of the lysosomal storage diseases. It is due to a deficiency of beta-glucocerebrosidase, an enzyme derived mainly from the degradation of red blood cells and which catalyzes the transformation of a lipid glucocerebroside complex that accumulates in the tissues, leading to multisystem disease. This autosomal recessive disease is distributed worldwide [1]. At least three phenotypes have been described: types 2 and 3 are associated with neurological problems and lead to early death, while type 1, also called chronic non-neuropathic Gaucher disease is the most frequent. The prevalence of type-1 Gaucher disease is approximately 1/40 000 in the general population; it is most common in the Ashkenazi Jewish population, where the prevalence is 1/500 to 1/1000. Bone involvement, which may be the first sign of the disease, is a major complication of type 1 disease and leads to pain and disability [2]. The objective of this review is to explain the mechanisms leading to bone involvement in type-1 Gaucher disease, describe the clinical bone manifestations and the utility of various assessment procedures, and analyze the bone benefits of two different types of treatment – one of the enzyme deficiency (either enzyme replacement therapy or miglustat), the other of its effects on bone (bisphosphonates).

Pathophysiology of osteoarticular lesions

A genetic deficiency of beta-glucocerebrosidase causes glycosphingolipids to accumulate in lysosomes of reticuloendothelial system cells, especially macrophages [3]. The abundance of macrophages in the bone marrow explains the frequency of bone damage in Gaucher disease. These intramedullary macrophage deposits have two principal consequences: volume expansion within the marrow and abnormal synthesis by macrophages of proinflammatory cytokines.

Glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>CETG</td>
<td>Committee to evaluate the treatment of Gaucher disease</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>DXA</td>
<td>dual energy X-ray absorptiometry</td>
</tr>
<tr>
<td>ERT</td>
<td>enzyme replacement therapy</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>QCSI</td>
<td>Quantitative Chemical Shift Imaging</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumor necrosis factor α</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>

Intramedullary volume expansion

The abnormal expansion of the intramedullary content causes bone thinning and deformation that explain the weakening of some peripheral bones. Locally, this compression promotes trabecular resorption that leads to cortical thinning and to lytic lesions that vary in their location and organization. Pressure on the cortical bone and modifications in the functioning and balance of osteoblasts and osteoclasts prevent the physiologic modeling that should occur during bone growth. The modeling that causes the metaphyseal tubulation of the long bones does not occur and the Erlenmeyer flask deformity develops (figure 1). Moreover, intramedullary macrophage expansion promotes extrinsic compression of the intraosseous feeding vessels and in turn results in ischemia. Depending on the site, this may cause either epiphyseal osteonecrosis (with possible subchondral bone and joint surface collapse that may produce secondary osteoarthritis) or bone infarction – either metaphyseal or diaphyseal (and the osteosclerotic healing, associated with peripheral intramedullary calcifications of the necrotic area – permanent calcifications clearly visible on plain radiography).

Beyond the extrinsic vascular compression, other mechanisms are suspected of promoting ischemia: vasospasms associated with the focal synthesis of proinflammatory cytokines [4], prothrombotic coagulation disorders [5], or spontaneous or posttraumatic localized intraosseous hemorrhages [6], promoted, for example, by thrombocytopenia. The perilesional healing of bone ischemia is due to an hypervascularized granulation tissue, and this congestion may promote secondary superinfections with osteomyelitis [4].

Abnormal cytokine synthesis

The accumulation in macrophages of glycolipids appears to activate and induce synthesis of cytokines (IL-1β, IL-6, IL-8, IL-10 and TNFα) and of lysosomal enzymes that activate osteoclasts (by up-regulation of cathepsin K) [7-11]. Activity of the osteoclast-osteoblast system may be modified because these proinflammatory and pro-osteoclastic cytokines promote lytic phenomena – mainly localized but also diffuse. The ensuing low bone mineral density (BMD), which varies substantially in intensity, may lead to generalized osteoporosis and its corollary, secondary fractures, especially in the trabecular bone (spine).

This pathogenesis of bone pain in Gaucher disease explains the heterogeneity and especially the nonspecificity of the osteoarticular lesions and the coexistence of focal lytic lesions, diffuse demineralization, and condensing lesions, which reflect perile- sional postischemic osteosclerosis.
Osteoarticular manifestations of Gaucher disease in adults: pathophysiology and treatment

Clinical manifestations of osteoarticular involvement

Osteoarticular symptoms and history vary substantially between patients, because of the chronic nature and unpredictable progression of Gaucher disease [12]. Age at symptom onset averages 20 years, but ranges from 2 to 80 years. Bone involvement is aggravated after splenectomy [13]. Osteoarticular involvement is not related in extent or intensity to damage in other organs.

Pain

Before any treatment, 63% of patients complain of bone pain. They report four different types [14]:
- moderate nonspecific pain of unknown origin for several days, which resolves without treatment;
- severe acute pain, regardless of site, called a “Gaucher crisis”: it is associated with bone ischemia and often necessitates strong opioids for 2-4 weeks;
- more moderate, often progressive, pain, associated with vertebral fractures due to trabecular impaction or progressive peripheral fractures of abnormal bones;
- chronic pain that may appear to be either articular and mechanical, suggestive of osteoarthritis (secondary to epiphyseal necrosis), or spinal and mechanical (related to small postfracture hyperkyphosis, affecting the trunk).

The intensity of pain during ischemia and the arthrogenic consequences of subchondral epiphyseal ischemia in young subjects produce serious consequences on the locomotor system and mobility. All bones may be involved, including flat bones such as the mandible [15] and axial skeleton; this can lead to diagnostic error (for example, suggesting spondyloarthropathy for sacral involvement) [16]. The bones most frequently involved are the femur, vertebra, humerus and tibia, with predominancy in the lower limbs. Symptoms in the ankle and foot begin most often in adolescence and sometimes reveal necrosis of the talus [17]. Nonetheless the upper limbs are involved in 30% of cases. Damage may sometimes be limited to necrosis of the capitate bone or swelling of the proximal interphalangeal joints, or these may simply be the initial disease symptom [18].

Overall, 33% of patients report painful bone crises before any treatment [14], crises most frequent during the first 20 years [4]. They occur especially in patients whose Gaucher disease is diagnosed before the age of 10 years and in those who have had splenectomies. The pain may be projected by joints or bone (peripheral or spinal), associated with a fever greater than 38.5°C, inflammation and an elevated white blood cell count that may reach 17 000/mm³ [19]. Acute osteomyelitis must be ruled out as a differential diagnosis, especially since congestion of the reactive perinecrotic granulation tissue may promote a spontaneous bacterial graft on the necrotic site [4].

Pathologic fractures

Fractures of the appendicular skeleton can occur spontaneously for minor injuries in areas weakened by ischemia or specific marrow infiltration with focal lysis. Similarly spontaneous vertebral fractures may occur in children or adults [19, 20] reducing their height by shortening the trunk or permanent hyperkyphosis but also potentially compressing roots or spinal cord.
Infections

Osteomyelitis is rare. Because it may occur secondary to a surgical procedure or biopsy, fewer bone marrow biopsies should be done, and all surgical procedures must be performed by experienced surgeons under strictly aseptic conditions [4, 21]. Osteomyelitis can also spontaneously complicate a bone crisis associated with acute ischemia [4].

Disability and impact on quality of life

The principal causes of morbidity and invalidity in patients with Gaucher disease are its osteoarticular manifestations, because articular limitations and prosthetic replacements (8%) require hospitalization and rehabilitation and have important occupational repercussions for these young people [14]. Moreover, prostheses are placed earlier than in the general population (the first hip prostheses took place at 43.8 years in the series by Lebel et al. with results as good as in the general population) [22]. Their impact on quality of life is unquestionable, as several studies show. Thus, the analysis of 602 patients in the International Gaucher Registry showed that 21% of the patients have some degree of disability: 12% walked with some difficulty, 7.1% required an orthopedic aid for walking and 1.2% a wheelchair, while 0.5% were bedridden [23, 24]. These data were corroborated by a study of 128 patients, in which 14% reported problems walking on flat ground, 23% a history of fractures, 32% a hip prosthesis, and 5% knee surgery [25]. The psychological consequences are clear: depressed mood and somatic concerns may follow. These psychological complications are similar to those of patients with other chronic diseases [26].

Sidebar 1
Recommendation on bone evaluation and monitoring in Gaucher disease

Initial evaluation before treatment
- Plain radiography (lateral view of spine, anteroposterior view of femora including femoral head and knees and all symptomatic sites)
- MRI: whole femora in coronal plane (T1- and T2-weighted)
- Bone densitometry (DXA) (spine, hip, forearm if appropriate)

Similar work-up to be repeated
- In absence of treatment: every 12-24 months
- Under stable treatment: every 24 months
- At dose change
- During clinically significant complication

DXA: Dual Energy X-Ray Absorptiometry


Radiologic abnormalities and the utility of various laboratory, imaging and genetic examinations

Radiologic bone manifestations are found in more than 95% of patients, and it is essential to identify them, both for disease screening and for its follow-up (sidebar 1) [24]. Nonetheless the frequency of radiologic signs depends on the imaging method used. MRI is the most sensitive technique. It is essential to recall that no radiologic finding is pathognomonic for Gaucher disease; the diagnosis is therefore based on the combination of these signs with hematologic abnormalities (thrombocytopenia, anemia, etc.) or visceral signs (splenomegaly, for example), or both. Final confirmation requires a leukocyte assay of beta-glucocerebrosidase.

Plain radiography

Plain radiology makes it possible to view the basic lesions. A minimal radiologic work-up must include both entire femora, a lateral view of the thoracic and lumbar spine, and any symptomatic areas [27]. Several types of abnormalities can be detected:
- Erlenmeyer flask deformity, that is, a metaphyseal enlargement of the long bones caused by defective tubulation (figure 1), predominantly in the distal femur or the proximal tibia. This sign is present in 46% [14] to 69% [1] of cases;
- osteopenia, present in 42% of cases; only osteopenia exceeding 30% can be assessed visually (which makes radiologic screening of more moderate osteopenia difficult) [14];
- cortical thinning, or even endosteal scalloping (visible in the distal humerus in 11% of cases) [1];
- local areas of condensation or osteosclerosis, sometimes called “bone in the bone”: this serpiginous popcorn sclerosis (figure 1) is the calcified scar of the perimeter of metaphyseal or diaphyseal ischemia. In the epiphyseal area, the condensation may appear heterogeneous and subchondral and be associated with a crescent sign or even existing osteoarthrosis [28]. The frequency of osteonecrosis is thought to be around 17% at the femoral head and 9% at the humeral head [1];
- localized lytic foci, sometimes resembling pseudotumors that may erroneously suggest suspicious bone lesions [29]. This pseudomyelomatous presentation must be recognized in these patients, who have often had monoclonal gammapathies. Nonetheless, malignant bone disease (leiomyosarcoma, malignant epithelioid hemangioendothelioma) has been described in association with post-infarction lytic bone lesions [30, 31];
- fractures: their overall frequency is thought to be around 15% [14]. They affect the appendicular skeleton (in weakened areas, either lytic or necrotic), ribs and spine (11% of thoracic or lumbar vertebral fractures according to Zimran et al. [1]).

Although radiologic improvements are possible after treatment, the overall radiologic appearance changes little [32]. Moreover, some abnormalities are permanent, including sclerotic scars of
bone infarction, radiologic osteonecrotic lesions and vertebral fractures [33]. Plain radiology is nonetheless useful for a rapid evaluation of the femoral heads (is there avascular osteonecrosis?), femoral neck (fracture risk?), and vertebral bodies (fracture prevalence with or without risk of compression?).

**Bone scintigraphy (whole-body Tc-99m-MDP)**

Bone scintigraphy is useful for the diagnosis of bone infarction and focal bone lesions [34]. It is helpful to recall that several different images may be found: an overall increase in skeletal uptake, focal uptake (which may reflect a microfracture or the peri-ischemic scarring area) or finally reduced uptake, either in very lytic zones or corresponding to avascular, or even hemorrhagic, necrotic foci [35, 36]. That is, during the first three days of bone infarction, an area of low isotope uptake may be visible. Then the congestion of the perinecrotic granulation tissue will allow excess perilesional uptake to be viewed for several months. Bone scintigraphy is very sensitive but only slightly specific. It will therefore show somewhat recent infarctions with a lower spatial resolution than MRI [35]. Other tracers have been used, including sestamibi, which provided interesting results, albeit difficult to interpret [37, 38].

**Computed tomography**

Computed tomography (CT) allows a detailed analysis of focal lesions by visualizing the exact distribution of the sclerotic areas and thus facilitates the differential diagnosis (figure 2). It can be useful when MRI cannot be performed but otherwise has no role in this evaluation [28, 39].

**Magnetic resonance imaging (MRI)**

MRI is the only noninvasive method that allows direct viewing of the bone marrow, since radiography and CT show only the effects of marrow damage on cancellous or cortical bone. Conventional MRI has a dual interest: it can be used to study the extent of marrow infiltration, especially in zones without any clinical manifestations, and to reveal the areas of avascular necrosis. The basic lesions seen in marrow infiltration are hypointense (dark) in T1-as well as 12-weighted sequences, and signal intensity does not increase after gadolinium injection. This indicates the disappearance of the normal marrow fat tissue, replaced by infiltrated tissue with a different structure. This marrow infiltration (seen in 40% of patients) may develop first in the axial skeleton and then the appendicular skeleton, with involvement predominantly in the lower and especially the proximal limbs [2, 14].

Besides analyzing marrow infiltration, MRI is highly sensitive in diagnosing all other bone consequences of Gaucher disease (for example, epiphysial osteonecrosis, either acute or after scar formation, and metaphysial or diaphysial bone infarction, also either in the acute phase or afterwards) (figure 3) [28, 35]. 12-weighted MRI is the most sensitive method for early detection of bone infarction during bone crises, as previously nonexistent signal brightens [4, 40]. The scarred zones, with fibrosis or infarction, are irreversible; signal intensity does not change, despite treatment. Nonetheless, while conventional MRI is extensively used for the initial evaluation and follow-up of complications, quantification of the infiltrate that would make possible its accurate monitoring under treatment has not been standardized. Scoring systems exist, but vary greatly according to team and country [41, 42]. For this reason, experimental MRI techniques have been developed to assess the degree of bone marrow infiltration; they aim principally at quantifying the marrow fat loss, which reflects the lipid-laden macrophage infiltration in Gaucher disease [39, 43]. Dixon’s test, known as quantitative chemical shift imaging (QCSI), is a “chemical” technique that owes its name to the chemical shift of the fat observed during MRI. The fat fraction and especially the triglyceride/water ratio are quantified precisely and the results expressed on a colorimetric scale. Nonetheless, this noninvasive technique is still experimental and limited to very rare centers. Another method, called bone marrow burden, has been proposed; it calculates a lumbar score related to presacral fat as the reference and modulates the score as a function of diffuse or heterogeneous signal [43]. The same type of analysis has also been proposed with the intervertebral disk signal used as the reference [44].

**Bone densitometry**

According to WHO, dual-energy X-ray absorptiometry (DXA) is the reference method for measurement of bone mineral density and assessment of the risk of fractures due to postmenopausal
osteoporosis. This method has been extended to other bone-
weakening diseases that promote fractures. We recall briefly
that osteoporosis is characterized by a bone mineral density
(BMD) at the lumbar spine and/or at the femoral neck more
than 2.5 standard deviations below than the mean for young
adults (T-score < -2.5) and osteopenia by a T-score between -1
and -2.5. This T-score is difficult to use in studies that pool popu-
lations whose ages range from late adolescence to 60 years
or older. In this case, to be able to interpret the densitometric
data, we use the Z-score (standard deviation compared with the
mean of subjects of the same age).

In a study of 61 adults aged 22-77 years with Gaucher disease,
Pastores et al. demonstrated that the mean bone mineral den-
sity − at the lumbar spine, femur, and radius − was significantly
lower than expected for age and sex and that this osteopenia
was significantly correlated with severity of both disease and
radiologic bone damage [45]. Another cross-sectional study of 12
patients found osteopenia at all sites [46]. Pretreatment inclu-
sion data for a longitudinal study of 10 patients found Z-scores
for the lumbar spine of -2.27 and for the femur of -1.78 [47].
Although bone density testing makes it possible to quantify
osteopenia, its predictive value for fracture risk in Gaucher
disease remains to be established. Moreover, its interpretation
may be distorted by the presence of vertebral collapse, prosthe-
tic material, or osteosynthesis.

Markers of bone remodeling

The new biomarkers of bone remodeling – markers of both for-
mation (osteocalcin, and total and bone alkaline phosphatases)
and resorption (C or N-terminal telopeptides in type 1 collagen)
– may be interesting in Gaucher disease because they make it
possible to approach bone remodeling more dynamically than
with the standard phosphate and calcium measurements. They
are already used during initial evaluation for postmenopausal
osteoporosis and in some cases to assess early response to
osteoporosis treatment, at 6 months.

Their practical use in Gaucher disease, however, remains to
be determined. In a pilot study of 10 patients, Ciana et al.
[48] found the bone formation markers significantly lower in
patients than in healthy subjects, while the bone resorption
markers were significantly elevated; that is, the course of bone
formation and resorption were dissociated. Drugan et al. [49]
did not confirm this finding, but instead observed a significant
concomitant reduction in both formation and resorption. These
still very fragmentary and discordant results do not allow us to
use and interpret these markers for bone monitoring in Gaucher
disease.

Treatment

The objectives of Gaucher disease treatment in adults are
threefold: provide functional relief, improve quality of life, and
prevent complications. There are specific treatment objects for
osteoarticular involvement [50]:
• diminish or eliminate bone pain within 1-2 years
• prevent painful bone crises
• prevent osteonecrosis and subchondral fractures
• increase trabecular bone mineral density within 3-5 years.

In addition to symptomatic treatment (analgesics, nonsteroi-
dal antiinflammatory drugs, bisphosphonates, and orthopedic
management of fractures or osteonecrosis), there are currently
two specific treatments available for Gaucher disease: imigluc-
erase (Cerezyme®) and miglustat (Zavesca®). Imiglucerase is
enzyme replacement therapy (ERT), the reference treatment
for type-1 Gaucher disease. It is the genetically engineered
recombinant form of glucocerebrosidase, the enzyme whose
deficiency causes the disease. In 1996, imiglucerase replaced
alglycerase, a placent al glucocerebrosidase. Imiglucerase is administered intravenously, in sequential perfusions. The initial dosage is 60 U/kg body weight, administered every 2 weeks. The summary of product characteristics for imiglucerase states that "this drug is indicated as a long-term enzyme replacement treatment in patients with a confirmed diagnosis of type-1 or type-3 Gaucher disease who have clinically significant non-neurological disease manifestations including anemia (after exclusion of all other causes, such as iron deficiency), thrombocytopenia, bone abnormalities (after exclusion of all other causes, such as a vitamin D deficiency), hepatomegaly or splenomegaly."

Miglustat acts differently: it reduces the substrate to inhibit glucosylceramide synthetase and thus decreases synthesis of glycosphingolipids and gangliosides. This drug is available in 100-mg capsules for oral administration, and the dosage in adults with type-1 Gaucher disease is one capsule three times/day. The summary of product characteristics describes the indication as follows: "Miglustat is indicated for the oral treatment of mild-to-moderate type-1 Gaucher disease. This drug must be used only for the treatment of patients for whom enzyme replacement therapy is unsuitable."

Currently no randomized study has assessed either ERT or miglustat in the treatment of bone complications in type-1 Gaucher disease. Table I summarizes the data available today. Nor has any study prospectively compared high-dose and low-dose ERT. Nonetheless the osteoarticular benefits with high doses do not appear to be better than with low doses [51], except perhaps for BMD.

Efficacy for bone pain

The first publications, in the early 1990s, showed the efficacy of ERT (alglycerase at that time) but did not specifically assess its effect on pain. It was thought, however, that it would take at least three years before radiologic improvements could be documented [52, 53]. In a prospective series of 33 patients, all with more or less severe bone involvement, Pastores et al. [52] reported that bone pain episodes improved for most patients with alglycerase, both in intensity and in frequency. The report did not describe how they evaluated either pain or response to treatment. The 1995 report of a French cohort included 45 patients, 26 (58%) with signs of bone involvement [54]. After an average of 14 months of alglycerase treatment at a dose of 60 U/kg/2 weeks, the authors noted a subjective improvement for most patients in bone pain, beginning during the first year of treatment, and a substantial reduction in bone pain after 3-4 months of ERT. These were preliminary results and the method of pain assessment was not specified. Femoral pain recurred in two patients after 6-8 months of treatment. According to Elstein et al. [55], all 14 patients with Gaucher disease with painful bone symptoms and treated by alglycerase at a dose of 15 U/kg/2 weeks for 2-4 years reported significant improvement in bone pain. Fallet et al. also reported that ERT improved bone pain in a series of six patients [56].

These advantages were analyzed in more detail in the series of 1028 patients with Gaucher disease included in the international Gaucher disease registry [24]. The follow-up of 229 patients who complained of chronic bone pain at registry inclusion showed that 100 (44%) had no pain while under treatment during the first year. During the second year, 52% (67/128) had no pain, including 20 of the 73 patients who had reported bone pain during the first year. A new painful bone crisis during the second year occurred to only two of the 43 patients without any bone pain during the first year. The information from this international registry does not, however, allow us to assess the dose/effect relation or judge whether increased doses in patients with continued pain under treatment led to clinical improvement. Nonetheless, these very encouraging and convincing results point to the need for early treatment of patients with type-1 Gaucher disease and specific bone pain.

In the most recent study by De Fost [57], which compared two cohorts from two different European centers, one in Amsterdam treated with low-dose ERT (n = 49; median dose = 15-30 U/kg/4 weeks), the other in Düsseldorf, treated by higher doses (n = 57; dose median = 50 U/kg/4 weeks), the authors state that atypical bone pain persisted after 24 months of treatment in some patients in both groups, but no systematic analysis was performed. Our data from the French CETG (Committee to evaluate treatment for Gaucher disease) registry of 101 patients treated with ERT points in the same direction: bone pain scores decreased under enzyme treatment [58]. There are no data currently available about the effect of miglustat on bone pain [59]. An open study administered miglustat to 10 patients, some ERT-naïve, others who had not taken ERT for three months, for various reasons. After 12 months of miglustat treatment, the four patients who complained of moderate bone pain at the beginning of treatment remained stable [60]. We do not know if these four patients were or were not ERT-naïve at the onset. Very recent unpublished data suggest that painful bone crises diminish in patients on miglustat, beginning during the first year. The benefit appears to continue during the second year, both in patients treated earlier by ERT and in treatment-naïve patients [61], but these data must be confirmed.

Effects on bone mineral density

If ERT reduces the number of Gaucher cells in the bone marrow, it may promote the loss of bone mineral content in men and woman of reproductive age, at least during the first months of treatment. Rudzki et al. [62] thus reported that in 4 of 5 patients treated by imiglucerase for 26-32 months, trabecular bone diminished, with a mean annual volume loss on the order of 16.06%. This mechanism may be explained by an increase in osteolytic activity due directly or indirectly to regenerating
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug tested and dosage</th>
<th>Population with bone symptoms</th>
<th>Duration of treatment</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imiglucerase: 20-60 U/kg/2 weeks</td>
<td>N = 33</td>
<td>6-24 months</td>
<td>Improvement in most patients (intensity and frequency of crises)</td>
<td>Pastores et al. [52]: OPS</td>
</tr>
<tr>
<td></td>
<td>Alglucerase: 60 U/kg/2 weeks</td>
<td>N = 26</td>
<td>14 months mean</td>
<td>Subjective improvement in pain from 1 year important diminution or reduction of crises after 3-4 months treatment</td>
<td>Belmatoug et al. [54]: RS</td>
</tr>
<tr>
<td></td>
<td>Alglucerase: 15 U/kg/2 weeks</td>
<td>N = 14</td>
<td>2-4 years</td>
<td>Improvement in bone pain in all cases with reduction in frequency and/ or intensity of crises or disappearance; benefits within 6 months</td>
<td>Elstein et al. [55]: RS</td>
</tr>
<tr>
<td></td>
<td>Alglucerase: 30-50 U/kg/2 weeks</td>
<td>N = 6</td>
<td>6-12 months</td>
<td>Reduction in intensity and/or frequency of symptoms in all cases</td>
<td>Fallet et al. [56]: RS</td>
</tr>
<tr>
<td></td>
<td>Alglucerase or imiglucerase: dosage unspecified</td>
<td>N = 229</td>
<td>6-60 months</td>
<td>Disappearance of bone pain in 44 and 52% of cases during 1st and 2nd years of treatment</td>
<td>Weinreb et al. [24]: RS</td>
</tr>
<tr>
<td></td>
<td>Miglustat: 100 mg x3/d</td>
<td>N = 4</td>
<td>12 months</td>
<td>Stability of bone pain</td>
<td>Pastores et al. [60]: OPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imiglucerase: 30 U/kg/4 weeks</td>
<td>N = 10</td>
<td>24 months</td>
<td>Diminution of BMD during first 3-6 months then improvement</td>
<td>Lebel et al. [47]: OPS</td>
</tr>
<tr>
<td></td>
<td>Imiglucerase: 6.5-30 U/kg/2 wk</td>
<td>N = 11</td>
<td>4.4-6 years</td>
<td>BMD improvement after mean 4.5 years</td>
<td>Ciana et al. [63]: OPS</td>
</tr>
<tr>
<td></td>
<td>Imiglucerase: 15, 30 or 60 U/kg/2 weeks</td>
<td>N = 160 patients</td>
<td>Up to 8 years</td>
<td>Improvement of at least 2 points in De Fost 1991-2002 after 24 months treatment in 12% of low-dose group and 33% of high-dose group patients in the low-dose group; significant difference in favor of the high-dose group in a subgroup of patients with more severe medullary infiltration</td>
<td>Wenstrup et al. [64]: RS</td>
</tr>
<tr>
<td></td>
<td>Alendronate: 40 mg/d versus placebo</td>
<td>N = 34</td>
<td>24 months</td>
<td>Significant BMD improvement in alendronate group</td>
<td>Wenstrup et al. [69]: Randomized double-blind study versus placebo</td>
</tr>
<tr>
<td></td>
<td>Miglustat: 100 mg x3/d</td>
<td>N = 7</td>
<td>12-24 months</td>
<td>No change in 4/7 with osteopenia or osteoporosis</td>
<td>Pastores et al. [60]: OPS</td>
</tr>
</tbody>
</table>

**Marrow infiltration**

- Group 1 (n = 9): calcitriol and calcium alone for 6 months then combined with imiglucerase.
- Group 2 (n = 10): calcitriol, calcium and imiglucerase.
- Group 3 (n = 10): imiglucerase alone.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug tested and dosage</th>
<th>Population with bone symptoms</th>
<th>Duration of treatment</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imiglucerase: 15-50 U/kg/4 wks versus</td>
<td>N = 49</td>
<td>Inclusion period: 1991-2002</td>
<td>Improvement of at least 2 points in inclusion marrow infiltration score after 24 months treatment in 12% of low-dose group and 33% of high-dose group patients in the low-dose group; significant difference in favor of the high-dose group in a subgroup of patients with more severe medullary infiltration</td>
<td>De Fost et al. [57]: retrospective study comparing two clinical practices</td>
</tr>
<tr>
<td></td>
<td>Imiglucerase: 60-120 U/kg/4 wks</td>
<td>N = 57</td>
<td>Inclusion period: 1991-2002</td>
<td>Improvement of at least 2 points in inclusion marrow infiltration score after 24 months treatment in 12% of low-dose group and 33% of high-dose group patients in the low-dose group; significant difference in favor of the high-dose group in a subgroup of patients with more severe medullary infiltration</td>
<td>De Fost et al. [57]: retrospective study comparing two clinical practices</td>
</tr>
<tr>
<td></td>
<td>Miglustat: 100 mg x3/d</td>
<td>N = 25, 10 ERT-naive</td>
<td>12 months</td>
<td>Diminution of medullary infiltration on MRI of 1-2 points after 12 months of treatment in patients naive to enzyme treatment</td>
<td>Giraldo et al. [71]: EOP</td>
</tr>
</tbody>
</table>

* Patients on imiglucerase 15-60 U/kg/2 weeks for at least 2 years.
** Imiglucerase: 60 U/kg/2 weeks for 6 months then 30 U/kg/2 weeks, calcitriol 0.25-3 μg/d and calcium 600 mg.

hematopoietic cells. In the open study reported by Lebel et al. [47], all 10 patients treated with enzyme therapy at a dose of 30 U/kg/4 weeks had a diminution in BMD during the first 3-6 months of treatment. After 18-24 months, this process was finally reversed in some patients, especially those older than 30 years, and BMD improved. Indeed, bone mass appears to improve under ERT only after a period of 3-4 years [63]. In an open series of 11 patients treated with doses from 6.5-30 U/kg/2 weeks for a mean duration of 4.5 years (range: 4.4-6 years), BMD improved significantly but only after 4.5 years; the mean Z-score rose from -0.81 to -0.56 (p = 0.005). Wenstrup et al. [64] reported results from the international registry for 342 patients treated with ERT only and 160 patients who did not receive ERT, all with lumbar spine BMD values available. These were all adults, with a mean age at their first bone densitometry of 36 ± 12 years for the population without ERT and 38 ± 13 years for those with it. Monitoring BMD for a duration of 8 years showed an improved Z-score among the treated patients over time, with a dose-response effect. The three most frequent protocols used 15, 30 and 60 U/kg/2 weeks and were correlated with an annual Z-score improvement of +0.064, +0.086 and +0.132 respectively.

The rather delayed effect of enzyme therapy on BMD led some physicians to prescribe bisphosphonates for some osteopenic or osteoporotic patients. After several encouraging anecdotal reports about pamidronate [65-68], Wenstrup et al. [69] found alendronate could be useful in their population of 34 adults (10 men and 24 women). This randomized, double-blinded, placebo-controlled trial included patients who had been receiving ERT for at least 2 years at doses ranging from 15-60 U/kg/2 weeks. Patients with an initial BMD Z-score >-1 were excluded from the study, except for several patients considered clinically at risk. Of the 36 patients randomized, 2 withdrew from the study during the first six months. The other 34 patients completed the study: 17 in the alendronate (40 mg/d) group and 17 in the placebo group. Bone densitometry showed a significant variation in BMD by the sixth month of alendronate treatment. At 24 months, BMD had increased by +0.0726 ± 0.0187 g/cm² in the alendronate group while it fell by -0.006 ± 0.005 g/cm² in the placebo group (p = 0.0053). They observed no radiologic modifications, in particular, focal lesions or bone deformations, in either group, at the end of the treatment period. Although the alendronate dose usually recommended for menopausal women is 10 mg/d, the dose chosen in this study – 40 mg – was based on a finding that this high dose was more effective than a dose of 20 mg in reducing focal lesions in Paget disease. This study thus confirmed the usefulness of bisphosphonate treatment in adults treated with enzyme replacement treatment who have fractures or a high fracture risk (osteopenic and/or osteoporotic on densitometry, with clinical risk factors for fracture). Nonetheless, because of the very prolonged accumulation of bisphosphonates in bone and the profound skeletal remodelling during pregnancy, which can lead to a fetal bisphosphonate burden that creates potential bone risks, it is appropriate to remain prudent for young women likely to become pregnant later. Bisphosphonates are contraindicated during pregnancy. Long-term data on the effect of miglustat on BMD are not currently available. Pastores et al. [60] conducted an open study of efficacy and tolerance in seven patients treated by miglustat for 12 and 24 months: four had densitometry-defined osteoporosis or osteopenia at study entry. These measurements neither improved nor worsened for any of the patients during the treatment period. These four patients, like the other patients in that study, did not want to or could not take ERT or had stopped ERT for at least three months. Because the article did not specify if the four osteopenic or osteoporotic patients were or were not ERT-naive, we cannot assess the effect of miglustat on BMD.

Effect on bone marrow infiltration

The number of Gaucher cells infiltrating the bone marrow clearly decreased in patients under ERT, as confirmed in several cases by biopsy after approximately two years of treatment [62]. Because reconstitution of the marrow fat content has been shown by a variety of MRI techniques, it is unfortunately difficult to compare studies. This reconstitution appears to be well correlated with a diminution in liver and spleen volume [70]. Moreover patients without marrow response also showed no diminution in liver or spleen volume. Nonresponders were found in both the high-dose and low-dose enzyme treatment groups. Schiffmann et al. [71] used Dixon’s test in a randomized study of 29 asplenic patients ERT-naive at the beginning of the study. They showed that ERT at a dose of 60 U/kg/2 weeks increased the marrow fat fraction by the sixth month of treatment. Using the bone marrow burden technique, de Fost et al. [57] found that high-dose ERT (80 U/kg/4 weeks) produced no better effects than with lower doses (15-30 U/kg/4 weeks), except in the small subgroup of patients with severe marrow improvement scores: 13 patients classified as severe in the low-dose treatment group and 22 in the high-dose group. An improvement of at least two points in the marrow burden score on MRI was observed in 10% of the low-dose subgroup compared with 33% of the high-dose group (p = 0.04). The longitudinal follow-up with Dixon’s test showed that the marrow fat fraction increased under ERT for at least the first 5-6 years [41]. Stopping enzyme treatment was accompanied by a reduction in marrow fat infiltration although hemoglobin and platelets remained stable for more than a year. This reduction in fat infiltration testifies to the change in disease even before any hematopoietic effect. Miglustat also appears to reduce marrow infiltration by Gaucher cells, as shown in two patients after three years of treatment [72]. Giraldo et al. [73] conducted an open prospective study by of 25 patients with mild to moderate Gaucher disease (10 naive to all treatment and 15 who had previously had ERT). After 12 months of miglustat treatment, marrow infiltration...
diminished. Specifically, the semi-quantitative MRI score in the naive subgroup showed an improvement of 1-2 points compared with the initial evaluation.

Prevention of osteonecrosis and subchondral collapse

There are so far no published data or quantitative results that indicate whether specific treatment for Gaucher disease can prevent osteonecrosis and subchondral fractures. The several cases reported in the literature are anecdotal, with contradictory results. In most of the 26 patients with bone damage in the French series reported by Belmatoug et al. [54], bone lesions, including bulky lytic lesions, substantial cortical resorption, vertebral fracture, and osteonecrotic zones were unchanged after two years of treatment. New osteonecrosis sites reported under enzyme treatment most often occur on preexisting bone damage [74].

Conclusion

The very frequent osteoarticular complications during Gaucher disease have major consequences on patients’ quality of life and thus require physicians to assess bone involvement rigorously. The pathogenic mechanisms are multiple but the increased volume of deposits (with extrinsic compression of vessels) predominates, together with increased synthesis of proinflammatory cytokines. No radiologic abnormality is pathognomonic for Gaucher disease. Rather, the combination of these radiologic abnormalities (in particular, postischemic) with cytopenia or organomegaly suggests the diagnosis. MRI is the most sensitive method for assessing and monitoring marrow infiltration, which is assessed at the femur but can also be tested at the lumbar spine (axial marrow) [77]. According to the most recent guidelines, all patients with type-1 Gaucher disease should have an initial bone evaluation that ideally includes MRI of the complete femora in the coronal plane (T1- and T2-weighted), plain radiography (including spine profile, and the femora in anteroposterior view, including the femoral heads and the knees and any other symptomatic site) and DEXA (spine, hip, and even forearm). Bone damage must be monitored regularly, with examinations every 1-2 years, or more often in cases of active osteoarticular disease. On the basis of the studies currently published, imiglucerase must be proposed as a first-line treatment in type-1 Gaucher disease with osteoarticular manifestations. The most recent guidelines, based on the German experience, are reported in sidebar 2 [77]. The role of miglustat in the treatment of bone damage in type-1 Gaucher disease must still be evaluated. Specific management for fracture risk, by bisphosphonates especially, deserves discussion on an individual basis.

Conflicts of interest: Rose-Marie Javier has received fees during the past 12 months from Abbott and Roche Laboratories. Eric Hachulla has received fees during the past 12 months from Actelion, Genzyme, Pfizer, Roche and LFB laboratories. The authors received no fees for the writing of this article.
References


