LDRTC News

Lysosomal & Rare Disorders Research & Treatment Center Newsletter • Issue 7 • February 2023

Letter from the Director

Ozlem Goker-Alpan, MD

We are presenting our 2023 newsletter, which is a synopsis of the latest news of the research conducted at LDRTC. We are looking ahead to our teamwork to bring new understanding to the different aspects of lysosomal diseases and unravel new treatment options for patients with rare disorders.

Over 300 million people and families around the world are directly affected by a rare disease. The month of February is special for the rare disease community. This is when we raise awareness and celebrate the lives of those affected by these serious and not well-understood disorders. At LDRTC, our mission is to bring the rare disease patients reasons to be hopeful for the future.

LDRTC is a unique institution with a dedication to improving the lives of individuals with LSDs and other rare diseases by providing clinical services, access to a variety of clinical trials, and bench-to-bedside projects with clinically meaningful outcomes. We are able to spend days, if needed, with the patients and families to understand the root of the issues and offer help with a whole-listic approach. In today's health care system, where the clinical services are compensated by the third party payors, care is limited to a maximum of 54 minutes (a level 5 clinical visit); this could be considered utopic. In 2023, the theme for Rare Disease Day was "equity," with a proposed definition of social opportunity, non-discrimination in education and work, and equitable access to health, social care, diagnosis, and management for patients with rare disorders. Health equity for patients is only conceivable by outcomes consequential to early diagnosis and expert clinical management, a rarity even with any developed country standards. Disorders are expensive diseases that the payors try to run away from. Thus, the care of a patient with a rare disorder becomes a saga with many interruptions and fractured medical services. Not the physician but the insurance companys' flow chart decides how the patient is managed and treated. We "experts" deal with the rabbit hole of continuous denials and appeals.

The gaps in healthcare for patients with lysosomal disorders are further augmented by the paucity of experts to train the medical community. Similarly, generating experts and mentors in the field is not only expensive but time-consuming. From the health care provider's perspective, it requires self-sacrifice and altruism. For the younger trainees who are after work-family balance, the gravity of the diseases, the complexity of the care, and the lack of fair compensation make rare diseases not an attractable professional choice.

For more than two decades that I've been working with families and patients with lysosomal disorders, I've witnessed many struggles while they go through this long journey called life. I feel privileged to know these warriors, big and small, who are the personification of endurance and resilience. All of this makes it worth every minute that we spend with and for the patients, giving true meaning to our existence professionally. While the rare community continues with its fight for a better tomorrow, LDRTC will always be by its side!

Thank you.

LDRTCNews is produced by the Lysosomal & Rare Disorders Research & Treatment Center.

Ozlem Goker-Alpan, MD
Founder and CMO

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Contents

Ambroxol and Lysosomal Storage Disorders

Ozlem Goker-Alpan, MD

Lysosomes are cytoplasmic organelles designated to digest waste and cellular debris. Proper functioning is essential to the cells' ability to metabolize and eliminate harmful materials. The major lysosomal pathway, also referred to as autophagy lysosomal pathway (ALP), is a cellular clearance pathway serving as the primary source for organelle turnover and clearance of unwanted proteins through proteolysis. However, the role of lysosomes is not only limited to housing proteolytic enzymes: they also participate in calcium signaling, trafficking organelles, nutrient sensing, and mitochondria repair (Osellame, 2014). The degradation of damaged mitochondrial proteins through autophagy is considered to be a significant function of the lysosomes and is called mitophagy. Mitophagy is initiated by the damaged mitochondrion itself, which is ultimately degraded by the macroautophagic pathway to compensate for energy shortage. One of the important stress signals for autophagy activation is environmental stimulation by, for example, pharmacological agents or energy crisis due to intracellular defects of metabolism. The key step in autophagy is the fusion of autophagic vacuoles with lysosomes to form autophagolysosomes, where the macromolecular components are broken down into metabolites that feed into the mitochondria to provide ATP for survival (Gomes, 2011). Therefore, functional lysosomes are essential for autophagy, energy balance, and mitochondrial metabolism. It is very well documented that ALP function is impaired in lysosomal storage disorders, in addition to the secondary biochemical processes, including the energy metabolism shown to be impacted (De la Mata, 2016).

Inflammation plays an important role in the pathophysiology of lysosomal storage disorders. It has been shown that the genes regulating the inflammatory response, such as though macrophage activation, are shared with the ones that regulate the autophagy pathway (Greene, 2022). It has been postulated that chronic inflammatory response and proinflammatory cytokine production due to the stored substrate further drives the substrate production and results in disease progression. The opposite is true, when the inflammation and secondary cytokine production are inhibited pharmacologically in animal models, the mice were protected from the adverse effects of the substrate storage and survived (Pandey, 2017).

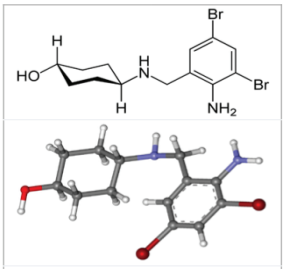
Lysosomal disorders are heterogeneous even among patients with the same disease, sharing similar genotypes. For example, in patients with Gaucher disease who are homozygous for L444(483)P variant, while the presentation is commonly of a young child with hepatosplenomegaly, low platelets and slowed saccades, the phenotypes may range from acute neuronopathic form to the lack of primary nervous system involvement. While a mutation in the glucocerebrosidase gene is required to cause Gaucher disease, other factors play an important role in the manifestation of the disease. Glucocerebrosidase is a lysosomal enzyme, synthesized on endoplasmic reticulum (ER)-bound polyribosomes and translocated into the ER. Following N-linked glycosylation, it is transported to the Golgi apparatus, from where it is trafficked to the lysosomes. It has been shown that mutant glucocerebrosidase variants present with variable levels of ER retention and ER-associated degradation (ERAD) in the proteasomes. The degree of ER retention and proteasomal degradation is suggested to be one of the factors that determine the severity of Gaucher disease (Ron and Horowitz, 2005).

Pharmacological chaperones (PC) are small molecules that can help to refold the mutated protein to prevent ERAD and proteosomal degradation. While a PC could help with ERAD, the main challenge is not only to enhance the enzymatic activity, but also further improve the downstream cellular processes, such as ALP pathway, mitophagy and mitochondrial functions, all of which will have an effect on protein folding, and further stabilize the intracellular environment. Inflammatory process is the common downstream pathway for all the LSDs. It has been recently shown that ALP functions and macrophage activation are regulated by the shared genes of the autophagy pathway.

Ambroxol (ABX) has been used as an over-the-counter drug for more than three decades in various countries, including Western Europe and Japan, as a mucolytic agent. There are various forms of Ambroxol such as tablets, syrup, and caplets of varying strengths, including an intravenous solution (Kantar, 2020). Ambroxol is a secretolytic agent, and a Na+ channel blocker (Gupta, 2010). In addition to its indication in both adult and pediatric patients with acute and chronic bronchopulmonary disease associated with impaired or abnormal mucous secretion or transport, in newborns, Ambroxol is also used for the treatment of airway mucus-hypersecretion and hyaline membrane disease (Hasegawa, 2006). Ambroxol inhibits

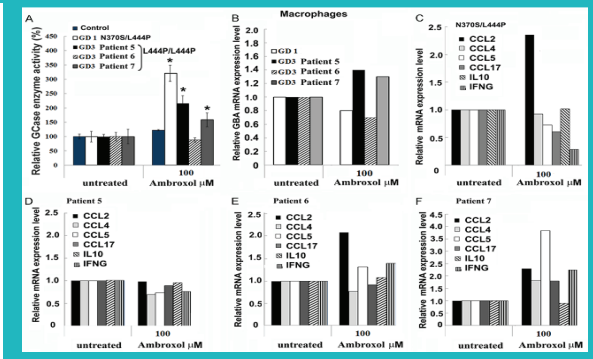
Ambroxol Chaperone Activity is Personalized

Ambroxol



Clinical data

AHFS/Drugs.com	International Drug Names (https://www.drugs.com/international/ambroxol.html)
ATC code	R05CB06 (WHO (https://www.whocc.no/atc_ddd_index/?code=R05CB06)) R02AD05 (WHO (https://www.whocc.no/atc_ddd_index/?code=R02AD05))



*Ivanova MM, et al. Am J Transl Res. 2018;10:3750-3761. Speaker's opinion.

* CCL, chemokine ligands; IFNG, interferon gamma; IL, interleukin; ND, no data; PBMC, peripheral blood mononuclear cell; ukec, urine-derived kidney epithelial cells; WT, wild-type.

both sodium currents through TTX-S and TTX-R, (Weiser and Wilson, 2002). Ambroxol increases the Cl(-)-dependent secretion. Ambroxol is an anti-inflammatory and immunomodulatory agent, and was shown to prevent inflammation through Th1 cytokines (Takeda, 2016) (Malerba, 2008).

Ambroxol is a mixed PC for *GBA1*, identified through screening using heat inactivation technique (Maegewa, 2009). Studies conducted in Japan and Korea using high dose Ambroxol in patients with neuropathic Gaucher disease showed that Ambroxol was safe and might help to arrest the progression of the neurological manifestations, as evidenced by enhanced residual GCcase activity observed in all patients. With high doses, there was decreased frequency of seizure activity and improved neurocognitive functions (Kim, 2020).

As ABX could fold *GBA1* protein to a more functional state, we asked whether patients carrying *GBA1* variants that are amenable to ABX chaperone activity present with phenotypes that vary for their given genotypes. *In vitro* response to Ambroxol was tested in PBMCs and/or fibroblasts and overall survival, and other morbidities were assessed in 12 children with genotypes predicting Gaucher disease type 2. In this cohort, the most common *GBA* variant was L444P(8/12). Ambroxol response was negative if GCase increased 20% or less and was associated with mortality by 24 months or ventilatory support, and positive if GCase activity was increased 100% or more, and a survival without tracheostomy beyond age 5 or mild delays and unassisted walking. This study shows that pharmacologic chaperones such as ABX could modify the Gaucher disease course, but also may aid in identification of attenuated forms through *in vitro* testing.

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Cardiac Imaging in Patients With Fabry Disease

Omar Abu Slayeh, MD

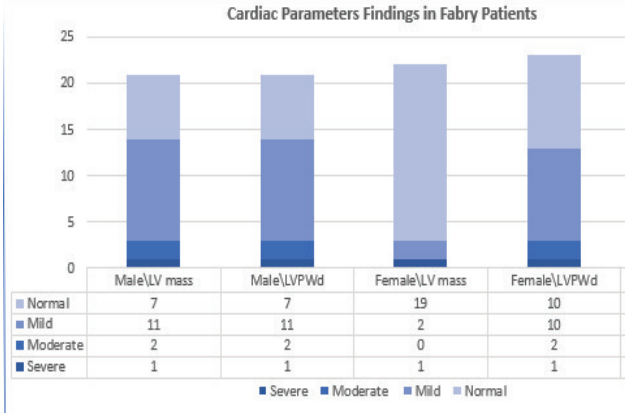
In Fabry disease (FD), α-galactosidase A deficiency leads to the accumulation of globotriaosylceramide (Gb3) and its metabolite lyso-Gb3, triggering a pathologic cascade that causes progressive damage to multiple organs. The cardiovascular complications are the most encountered morbidity, and are the leading cause of premature death.

In FD, chronic inflammatory response is one of the downstream events associated with the disease progression. In the cardiac tissues, the infiltration of lymphocytes and macrophages suggest that inflammation plays a significant role in cardiac damage in FD cardiomyopathy. NF-κB and TNF signaling pathways (MCP-1, INF, TGF-β) play a subsequent role in inflammatory response and the progression to fibrosis. Activation of coronary angiogenesis (VEGF) further plays a role in cardiac vascularization and pathological hypertrophy.

We studied 43 patients with Fabry disease and 20 healthy controls (10 males and 10 females with average age 48 ± 11 yrs). Clinical presentation, GLA activity and molecular analysis confirmed the diagnosis of FD. The subjects were further categorized into groups based on echocardiographic and cardiac MRI with late gadolinum enhancement (CMR/LGE) findings, left ventricular mass (LVM), and LVPWD measurements. The cohorts included: No cardiac involvement, or mild, moderate, and severe hypertrophic cardiomyopathy. Below are the main observations from this study:

1- In female patients: LVPWd can be more accurate to diagnose FD cardiomyopathy as LVM may remain within normal range due to asymmetric involvement of the heart
2- In male patients: The cardiac parameters, LVPWd correlate with LVM due to concentric hypertrophy.
3- While cardiac fibrosis is a finding associated with the progression of the FD cardiomyopathy in males. It may occur earlier in female patients with Fabry disease despite having normal cardiac parameters (LVM and LVPWd).
4- Cardiac MRI (CMR) with late gadolinum enhancement (LGE) is essential in assessing the patients with Fabry disease as it detects fibrosis and early cardiac involvement.

ECHOCARDIOGRAM AND/OR CMR FINDINGS IN PATIENTS WITH FD CARDIOMYOPATHY



STAGES OF HYPERTROPHIC CARDIOMYOPATHY (HCM)

WOMEN				
	Reference range	Mild	Moderate	Severe
LVPWd	0.6-0.9cm	1.0-1.2cm	1.3-1.5cm	>=1.6
LV mass	66-150g	151-171g	172-182g	183g

MEN				
	Reference range	Mild	Moderate	Severe
LVPWd	0.6-1.0cm	1.1-1.3cm	1.4-1.6cm	>=1.7cm
LV mass	96-200g	201-227g	228-254g	>=255

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This study is currently enrolling, has twelve screened, eight patients enrolled, and will continue through 2025.

Outcomes of Enzyme Replacement Therapy in Infants and Young Children With Gaucher Disease

Nazish Khan

Gaucher disease (GD) is an inherited metabolic disorder that causes an accumulation of harmful lipids, particularly glucocerebroside, and affects various organs, including bone marrow, spleen, and liver. This accumulation is caused by the absence or deficiency of the enzyme β-glucocerebrosidase. There are three types of Gaucher disease, GD Type I-Non neuronopathic (most common), GD Type II-Infantile (often fatal), and GD Type III-neuronopathic. Type I is the most common among people of Ashkenazi Jewish descent. Gaucher Disease affects approximately 1 in every 20,000 live births.

Enzyme replacement therapy (ERT) may aid in preventing GD complications when administered early. Velaglucerase alfa (VPRIV) is approved as an ERT for GD; however, administration parameters in very young pediatric patients remain unknown. This is a phase 4, observational, retrospective/prospective, non-controlled, non-comparative, single-center, single-cohort study that has the objective to determine if ERT improves growth and other GD-related symptoms in children who are four years old or younger. Each eligible patient's data is collected for at least 18 months and prospectively up to 36 months.

This study, which was initiated in January 2021, is currently enrolling, has eight patients enrolled, and will continue through 2025. One patient is five years old and has participated in the study for over 18 months. Most of the patients obtain their ERT via home infusions. The remaining patients visit their local clinics, hospitals, or LDRTC. All of the patients receive 60 to 80 units of ERT weekly or biweekly, and have shown an increase in growth, and improvement of GD-related signs and symptoms. There were no drug-related adverse events recorded. The data obtained from this study will help to assess the safety and effectiveness of ERT in young children, providing valuable treatment information for pediatric patients with Gaucher disease.

Goker-Alpan *et al.*, 101 World Symposium 2022

Case Report

Simultaneous Heart and Kidney Transplantation in a patient with Fabry Disease

Omar Abu Slayeh, MD

Fabry disease is an X-linked lysosomal disorder due to the deficiency of alpha-galactosidase A, that results in the accumulation of globotriaosylceramide (Gb3) in various tissues with progressive renal, cardiac, and cerebrovascular end-organ damage. The prevalence of Fabry disease (FD) varies from 1:17,000 to 1:117,000, but FD is underdiagnosed due to the nonspecific manifestations at the disease onset, and the low rates of suspicion for the disease because of the delayed complications.

We describe the case of a 59-year-old man with Fabry disease, who had chronic renal disease and systolic heart failure, who received a successful simultaneous heart and kidney transplantation. In the literature, renal transplant is described, and is offered to patients with Fabry disease who develop end stage renal disease. However, there is a very small percentage of patients who underwent heart transplantation. The patient was diagnosed with Fabry disease at the age of 27 and started on enzyme replacement therapy (ERT) since the diagnosis. The patient received his first kidney transplantation 6 years after the diagnosis of Fabry disease. Despite continued treatment with ERT, he had progressive worsening of FD cardiomyopathy with deterioration of the function of the transplanted kidney with an EGFR=17 (ref > or = 60mL/min/1.7 m2) and the ejection fraction (EF) was 30% on echocardiogram. A cardiac catheterization was performed, and showed no significant atherosclerosis in the left main coronary artery, left circumflex artery and right coronary artery. However, with moderate arm exercise during the catheterization, there was a significant decrease in LVEF. Due to the likely continued decline of the patient's renal and cardiac functions, he was placed on the transplant list. The patient received a successful simultaneous heart and kidney transplant when a compatible donor was found. After the transplant, the patient ejection fraction improved to 65%. The patient's estimated glomerular filtration rate was 50 mL/min/1.73m2. Post operatively, the patient continued on enzyme replacement therapy.

Comorbidities have an important impact on the decision about the acceptance for cardiac transplantation. Renal function is a very important risk factor for mortality post-transplantation. Irreversible renal dysfunction with a GFR less than 40 ml/min can be considered as a relative contraindication for heart transplantation, as renal function is expected to further deteriorate as a result of the nephrotoxic immunosuppressive drugs. The incidence of chronic renal failure after a heart transplant could be up to 20% or more with poor prognostic outcomes. Many patients may end up on dialysis after the heart transplants (Jonge, 2008).

Chronic renal insufficiency occurs commonly in patients with Fabry disease. In a case series from the National Institutes of Health, up to 50% of patients with Fabry disease developed chronic renal insufficiency, and 23% of patients developed end stage renal disease (ESRD). Treatment of patients with Fabry disease with ERT stabilizes and preserves kidney function. It is recommended to start treatment with ERT as early as the diagnosis of Fabry disease is made, as studies showed that ERT may be less effective when patients are in advanced stages of disease. It is reported that outcomes of kidney transplantation in patients with Fabry disease and the general population are comparable. Graft survival was similar in both populations.

Cardiac involvement in Fabry disease is common, and can manifest as coronary insufficiency, atrioventricular conduction

Comorbidities have an important impact on the decision about acceptance of patients for cardiac transplantation. Due to the rarity of Fabry disease, and the small percentage of patients who received heart transplantation, information on heart transplantation outcomes in Fabry disease is scarce.

disturbances, arrhythmias, valvular involvement, and cardiac hypertrophy. More research in the future is needed to elucidate the timing of the start of ERT in preventing cardiac dysfunction in asymptomatic or minimally symptomatic patients with Fabry disease. Due to the rarity of FD, and the small percentage of patients who had received heart transplantation, information on heart transplantation outcomes in this patient population is scarce. We found limited data on the long-term outcome of patients with Fabry disease who received a heart transplantation. One case report describes a patient who had good graft survival on follow up after 14 years. Like most, patients with Fabry disease may only be eligible for heart transplantation with end stage heart failure. However, other advanced therapies such, like left ventricular assist devices may not be employed due to the small left ventricular cavity diameter due to hypertrophic cardiomyopathy. This case demonstrates that patients with Fabry disease could be candidates for heart transplantation earlier than anticipated. Multi-organ transplantation even if there is accompanying end stage kidney disease could be succesfully employed to save lives.

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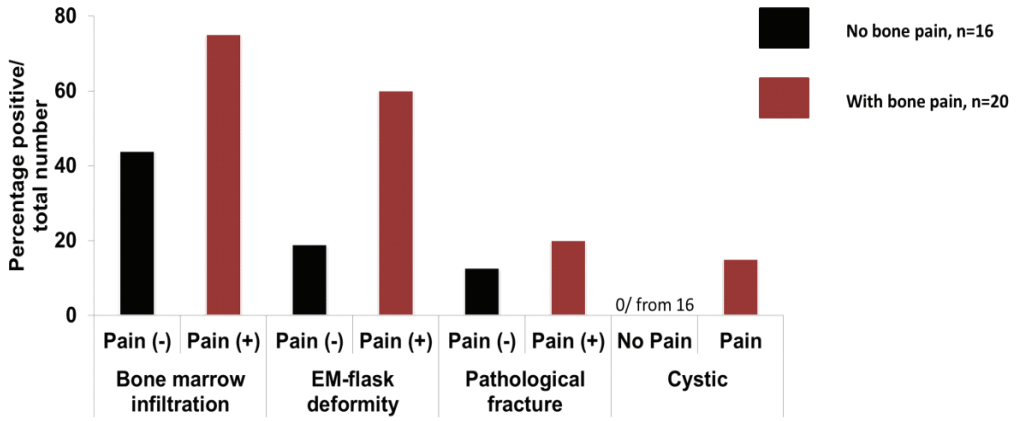
Approximately 75% GD patients develop skeletal complications:
* Avascular necrosis (AVN)
* Bone pain and joint pain
* Osteopenia and Osteoporosis
* Spontaneous fractures

'Erlenmeyer flask' deformity is one of early signs of GD bone pathology.

Patients With Gaucher Disease and Bone Pain Have Higher Rates of Bone Marrow Infiltration, Erlenmeyer Flask Deformity, Bone Fractures, and Cystic/Lytic Lesions



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Margarita M. Ivanova, PhD

Patients with Gaucher disease (GD) have progressive bone involvement that clinically presents with debilitating bone pain, structural bone changes, bone marrow infiltration (BMI), Erlenmeyer flask (EM) deformity, and osteoporosis (Goker-Alpan, 2011).

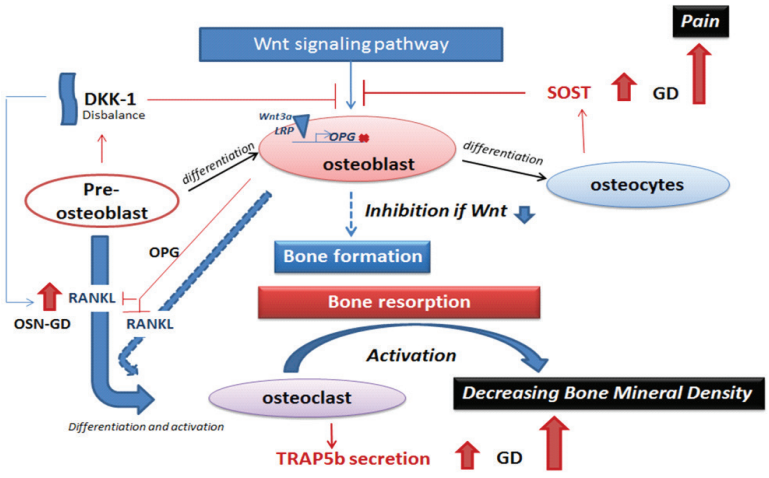
Skeletal disorders are often accompanied by bone pain. In GD, the pain may continue to persist despite of therapy. The source of bone pain is still debated as nociceptive pain secondary to bone pathology, neuropathic or inflammatory origins. Bone disease in GD is a sum of progressive events that begin with irregular bone development as defects of vertebral remodeling and EM flask deformity (Kaplan *et al*., 2006; Pastores and Meere, 2005). Bone destruction (osteonecrosis, cystic/lytic lesions), accompanied by the reduction of bone mineral density leads to osteoporosis at an early age (Itzchaki *et al*., 2004; Ivanova et al., 2021; Ivanova *et al*., 2022). Brief Pain Inventory analysis from our cohort revealed that 45% of GD patients with normal mineral bone density, 45% with osteopenia, and 78% patients with osteoporosis report chronic pain. These data are commensurate with the literature that 27-63% of patients with GD have a history of pain (Goker-Alpan, 2011; Ivanova et al., 2021; Oliveri et al., 2020; Reed et al., 2018). While it has been considered that pain is a result of skeletal involvement in GD, but in the absence of bone disease, pain could occur without a clear explanation. Thus, the source of pain could be chronic inflammation, structural damage to the peripheral nervous system and/or infiltration of Gaucher cells in the bone marrow.

Infiltration of Gaucher cells in the bone marrow leads to thinning of the cortex, osteonecrosis, lytic lesions, and may cause pain (Hughes *et al*., 2019; Linari and Castaman, 2015). In addition, bone marrow infiltration induces abnormal bone remodeling. The modeling disorder of the distal femurs, Erlenmeyer flask deformity, is a common radiological finding in patients with Gaucher disease (Faden *et al*., 2009; Linari and Castaman, 2015; Wenstrup *et al*., 2002).Erlenmeyer flask deformity implies the involvement in childhood when the skeleton is developing. This deformity, resulting from defective bone modeling at the meta-diaphyseal region, leads to straight uncarved di-metaphyseal borders and cortical thinning (Faden *et al*., 2009). However, cellular aspects of bone remodeling leading to EM-flask deformity are not fully understood. Several studies discuss that osteoclast impairment could be the cause (Adusumilli *et al*., 2021).

Wnt Signaling Pathway Inhibitor, Sclerostin, Is a Novel Biomarker of Bone Pathology in Gaucher Disease

Magarita M. Ivanova, PhD

Wnt signaling pathway inhibitor, sclerostin, is a novel biomarker of bone pathology in Gaucher disease. The dynamic communication between osteoclast, osteoblast, and osteocytes controls bone remodeling. Osteocytes coordinate osteoclast and osteoblast activity, acting as endocrine elements by secreting hormone-like mediators that affect bone cell function and respond to mechanical stimulation on bones (Gerosa and Lombardi, 2021). Sclerostin regulates bone formation by inhibiting osteoblast-osteocyte differentiation, decreasing bone matrix formation, promoting osteoblast apoptosis, and maintaining bone-lining cells in an inactive state (Figure 1) (Holdsworth et al., 2019; Kitaura *et al*., 2020; Sapir-Koren and Livshits, 2014; Tu *et al*., 2012). Additionally, sclerostin is an inhibitor of the Wnt signaling pathway and leads to the inhibition of bone formation. We recently reported the results from a study focusing primarily on the bone pathology and biomarkers in patients with Gaucher disease. We demonstrated that elevated levels of sclerostin in plasma correlated with pain in patients with GD. Moreover, the highest level of sclerostin was measured in GD patients with bone marrow infiltration and EM deformity. Overall, 95% of GD patients with pain, BMI, and EM deformity had increased levels of sclerostin and the majority of patients with elevated sclerostin, also had osteopenia or osteoporosis. This study may lead to an understanding of the connection between Wnt signaling pathway in bone metabolism and bone pain in GD.



Ivanova MM, Dao J, Kasaci N, Friedman A, Noll L, Goker-Alpan O. Wnt signaling pathway inhibitors, sclerostin and DKK-1, correlate with pain and bone pathology in patients with Gaucher disease. Front Endocrinol. 2022

Figure 1. A model of inhibition of the Wnt signaling pathway in Gaucher disease. The balance between bone formation and bone resorption is controlled by Wnt signaling pathway (activation of bone formation), sclerostin and DKK-1 (inhibition of bone formation), and the RANKL/OPG pathway (osteoclast activation). Elevation of secreted sclerostin or DKK-1 leads to inhibition of Wnt signaling pathway in GD. Sclerostin prevents activation of binding of Wnt 3a and LRP on the cellular membrane and, as a result, inhibits the expression of genes that stimulate bone formation, for example, RANKL inhibitor - OPG. RANKL, expressed by pre-osteoblasts and osteoblasts, promotes osteoclast maturation. Activation of osteoclasts initiates bone resorption. Elevated TRAP5b in GD plasma is the biomarker of osteoclast activity and activation of bone resorption. Activation of bone resorption with inhibition of bone formation leads to decreasing bone mineral density in GD. (Abbreviation: SOST-sclerostin, OSN-osteopenia). Figure. Ambroxol and Eliglustat induce lysosomal trafficking and LAMP1 level in primary fibroblasts. A-B. Fluorescence microscopy images of control fibroblast (A) and GD2 fibroblast (B). The cells were treated with 10 μM ambroxol (AMB) and 10 μM eliglustat (EGT) for five days. Each set of three side-by-side images shows anti-GBA (red), anti-LAMP1 (green color) antibodies, and merged images. The yellow color indicates colocalization of GBA and LAMP1 in the lysosome. (C) The interactive 3D color inspector plots displayed a three-dimensional graph of pixel distribution of images of GD2 fibroblasts. Nucleus (blue), GBA (red) and LAMP1 (green) colocalization.

Pharmacological inhibition of sclerostin by monoclonal antibodies as a potential therapy for osteoporosis

The most common therapies to treat bone pain are nonspecific such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opiates. “Bone Pain Inventory” analysis of our study showed that some of our patients used NSAIDS (such as ibuprofen), acetaminophen to treat pain, or, in instances of more severe pain, the management included opiates (Ivanova *et al*., 2022). While, NSAIDs can be effective to relieve bone pain, for extended usage there are hepatic, renal, or other vascular effects. Opiates for long-term use have the risk of dizziness, vertigo, and development of dependence. Moreover, these therapies do not treat the source of the actual disease; they only inhibit pain. The treatment of bone disease and chronic pain in patients with GD is complicated and often insufficient. Inhibition of osteoclast activity may be a solution to inhibit bone resorption and reduce bone pain. Bisphosphonates and Denosumab were initially developed to treat osteoporosis, but both therapies relieve pain in patients with bone cancer (Fabre *et al*., 2020). Pharmacological inhibition of sclerostin by monoclonal antibodies has been explored as a potential therapy for osteoporosis, fracture healing, and other bone disorders (Fabre *et al*., 2020; Rauner *et al*., 2021). Anti-sclerostin antibodies were shown to improve bone mineral density or fracture healing and may relieve skeletal pain (Fabre *et al*. 2020; Frost *et al*., 2016; Mitchell *et al*., 2018). Our study suggests that the Wnt signaling pathway plays an important role in GD-associated bone disease, and sclerostin could be a valuable biomarker to monitor patients with GD. The pharmacological inhibition of sclerostin by monoclonal antibodies as a potential therapy for osteoporosis need to be further elucidated in GD.

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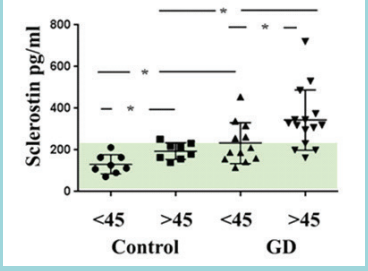
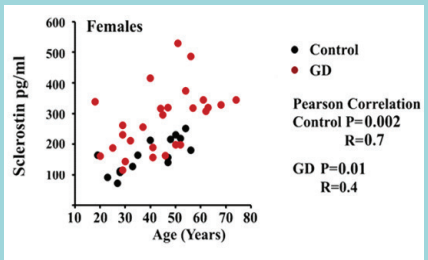
Sclerostin and age

Serum sclerostin levels increase with age, and are associated with declining bone formation, activation of bone resorption, and decreased bone mineral density (Coulson *et al*., 2017; Xu *et al*., 2020). Our study concurs that sclerostin levels increase with age in both healthy females and female patients with GD. However, sclerostin plasma levels are significantly higher with GD patients compared to age-matched controls (Figure 2). Moreover, GD patients have elevated sclerostin levels compared with healthy controls from the same age group. These observations correspond with the data that in GD, the structural bone changes, including early onset of accelerated bone mineral density loss, are less related to age (Goker-Alpan, 2011). Our data demonstrated that the average age of GD patients with normal bone mineral density is 34±12 years, with osteopenia is 46±17 years and osteoporosis is 47±14 years.



Sclerostin level in female controls and GD patients age-related; cohort divided into two groups before and after 45 years old. *Unpaired t-test p < 0.05.



Scatterplot analysis of the correlation of sclerostin and age in healthy controls and GD female. Pearson’s two-tailed correlation.

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LDRTC and CheckRareCE co-hosts Quarterly CME Series

Ozlem Goker-Alpan MD, opened the 2022 CME Series by presenting the Assessment of Biomarkers in Lysosomal Storage Diseases from a Mechanistic Approach. The lecture described the advantages and the limitations of biomarkers for LSDs. She also stressed the importance of newer, more targeted biomarkers for LSDs.

The CME Series continued on with Dr. Goker-Alpan and Neal J Weinreb, MD, speaking about Current and Emerging ERTs/SRTs and the way these two treatment options have transformed the LSD population. Both introduce the new research underway to improve the safety and efficacy of ERTs/SRTs, and how it is addressing the problem of the blood-brain barrier.

In the third webinar Ozlem Goker-Alpan, MD, invited Sonata Jodele, MD, to list Advances in Gene Therapy for Lysosomal Diseases. They introduced the limitations and unmet needs of the current therapeutic landscape for lysosomal disorders. Drs. Goker-Alpan and Jodele reviewed the gene transfer therapies for lysosomal disorders. They closed their talk by discussing the best clinical practices to monitor the safety profile of gene therapy and the best practices for gene therapies.

Dr. Goker-Alpan hosted the last webinar of 2022 with Oral Alpan, MD, exploring how the immune system is involved in Lysosomal disorders, reviewing the pathophysiology, best clinical practices to monitor and better manage patients with immune response reactions.

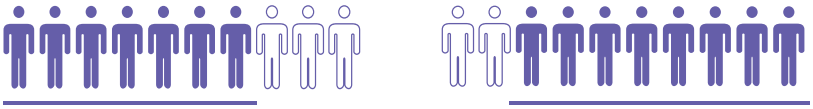
Highlights of CME Series 2022

Modules

- **Assessment of Biomarkers in Lysosomal Storage Diseases from a Mechanistic Approach**
- **Current and Emerging ERTs/SRTs**
- **Advances in Gene Therapy for Lysosomal Diseases**
- **The Immune System and Lysosomal Diseases**

GRID Symposium 2022 Highlights

Downstream Pathways and Lysosomal Storage Disorders from translational to clinical contexts



LDRTC hosted the 2022 Genetic, Rare & Immune Disorders Symposium (GRIDS) on November 20-21 in Fairfax, Virginia. This year's event focused on the "Downstream Pathways and Lysosomal Storage Disorders from translational to clinical contexts".

The symposium featured in-person and virtual presentations from researchers, physicians, and patient advocates from Brazil, Chile, Israel, Turkey, and the United States. During the first day of the event, experts in the field presented about basic mechanisms and model systems in Lysosomal disorders, the application of novel technologies, biomarkers and other genetic/genomic approaches in LSDs. On the second day, they addressed novel and new generation therapies in LSDs and current clinical management and challenges in LSDs.

Ozlem Goker-Alpan, MD, Founder/CMO of LDRTC, opened the symposium by highlighting the importance of this event and the reason behind the limited number of speakers. "It is a pleasure to host this annual event dedicated to the LSDs community. I've never intended for GRIDS to be a big symposium because I want this event to be a personal platform for experts in the field to exchange knowledge and showcase their latest findings that will eventually benefit our dearest LSDs community."

GRIDS 2022 ended with the Expert LSD clinic, where world-renowned physicians advised a select group of patients on their challenging disorders.

The 8th edition of the summit was the first in-person GRID Symposium since 2019, when the pandemic hit. Subscribers were also able to attend the event from home. If you are interested in reviewing the 2022 GRIDS, with CME lectures, please visit http://www.gridssymposium.org

AGENDA

BASIC MECHANISMS AND MODEL SYSTEMS IN LYSOSOMAL DISORDERS

- The control of degradation pathways and disease mechanisms in LSDs
- Catabolic pathways in animal models of GM2 and Tay Sachs Diseases
- Studying WNT canonical pathway using model systems in neuropathic LSDs
- Development of a precision medicine platform for uncovering genetic modifiers of Niemann-Pick type C disease

THE APPLICATION OF NOVEL TECHNOLOGIES IN LSDS

- Evolving insight about Pompe
- Multi-omic data in the diagnosis and treatment of LSDs
- Mimicking bone and cartilage disease using 3D bioprinting in Lysosomal Disorders
- An integrated platform for analysis of epigenomics and transcriptomics data

BIOMARKERS AND OTHER GENETIC/ GENOMIC APPROACHES IN LSDS

- New tool to interrogate the relationship between GBA1 and parkinsonism
- Quantitative neuroimaging in mucopolysaccharidoses clinical trials
- The value and validity of biomarkers – real world experience in GD
- Podocyte injury in Fabry disease in female and later-onset variant of the disease

NOVEL AND NEW GENERATION THERAPIES IN LSDS

- Current management of Pompe disease with new generation enzyme replacement therapies
- Brain penetrant ERTs
- Targeting glycogen synthase pathway in Pompe disease
- The biological activity and the effects of infused cyclodextrin on cholesterol metabolism in the CNS and peripheral tissues in patients with Niemann Pick C disease.

CURRENT CLINICAL MANAGEMENT AND CHALLENGES IN LSDS

- Are there advantages for early or pre-symptomatic therapy in LSDs?
- Risk assessment and mitigation strategies in gene therapies
- The GM1 and GM2 Gangliosidoses: Natural History and Current Therapy
- Parent and Family experiences with Newborn screening for LSDs and other inherited metabolic disorders

Genetic Rare & Immune DISORDERS SYMPOSIUM (GRIDS)

Genetic & Rare & Immune

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