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VIEWPOINT

Nutrition in adult patients with selected lysosomal storage diseases

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Abstract Lysosomal storage disorders (LSDs) are a group of clinically heterogeneous disorders affecting the function of lysosomes and are characterized by an accumulation of undigested substrates within several cell types. In recent years there have been substantial advances in supportive care and drug treatment for some LSDs, leading to improved patient survival, as seen in Gaucher, Pompe and Fabry disease and some Mucopolysaccharidoses; however, many symptoms still persist. Thus it is now even more important to improve patients' quality of life and reduce symptoms and comorbidities. One potential way of achieving this goal is through adjunct nutritional therapy, which is challenging as patients may be overweight with associated consequences, or malnourished, or underweight. Furthermore, drugs used to treat LSDs can modify the metabolic status and needs of patients. There are currently not enough data to make specific dietary recommendations for individual LSDs; however, suggestions can be made for managing clinical manifestations of the diseases, as well as treatment-associated adverse events. The metabolic and nutritional status of adult patients must be regularly assessed and individualized dietary plans may be created to cater to a patient's specific needs. Damage to the autophagic process is a common feature in LSDs that is potentially sensitive to dietary manipulation and needs to be assessed in clinical studies.

Abbreviations: AEs, adverse events; ASM, acid sphingomyelinase; ASMD, acid sphingomyelinase deficiency; BMD, bone mineral density; CKD, chronic kidney disease; CoQ10, Coenzyme Q10; CYP, cytochrome P450; DXA, dual-energy X-ray absorptiometry; ERT, enzyme replacement therapy; FD, Fabry disease; FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide and polyol; GAA, acid alpha glucosidase; GD, Gaucher disease; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; HSCT, hematopoietic stem cell transplantation; LSDs, lysosomal storage diseases; MPS, mucopolysaccharidoses; mTOR, mammalian target of rapamycin complex 1; NPD-A, Niemann-Pick disease type A; NPD-B, Niemann-Pick disease type B; NPD-C, Niemann-Pick disease type C; PD, Pompe disease (Glycogen storage type II disease); PLP, pyridoxal phosphate; *SMPD1*, sphingomyelin phosphodiesterase 1 gene; SRT, substrate reduction therapy.

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Introduction

Lysosomal storage diseases (LSDs) are a group of genetic disorders that affect the function of lysosomes, which are intracellular organelles responsible for the degradation and recycling of macromolecules and other cellular components [1–3]. Lysosomes play an essential role in regulating cell homeostasis and are also involved in autophagy, nutrient sensing, the immune response to infection, plasma membrane repair, regulation of cell receptors, cholesterol and glucose metabolism and bone remodeling [4,5]. Consequently, genetic mutations that alter the function of lysosomes can lead to a broad range of pathological conditions affecting many tissues and organ systems [1,4].

Although LSDs are clinically heterogeneous disorders, they are characterized by an accumulation of undigested substrates within the cell, activation of other metabolic pathways and responses which lead to cell destruction and organ damage [4]. LSDs are classified by either the deficient enzyme or by the chemical composition of the stored material [1]. Signs of LSDs typically appear in infancy or childhood, although attenuated adult-onset forms also occur; generally, symptoms develop progressively as the substrate accumulates; newborn screening may allow early patient diagnosis and treatment before severe damages occur [6]. As individual diseases, LSDs are rare; however, collectively they have an estimated incidence of 1 in 5000 live births [7]. The incidence is higher in certain ethnicities, often because of a founder effect or consanguinity [1]. Pilot studies investigating newborn screening for LSDs suggest that the incidence may be higher than previously estimated [6,8]. There has been substantial progress in LSD research and treatment in recent years [8]. The introduction of better supportive care and approved drug treatments for some LSDs has led to improved patient survival and has therefore increased the disease prevalence, at least in wealthier countries [1]. Currently available treatments include hematopoietic stem cell transplantation (HSCT), enzyme replacement therapy (ERT), substrate reduction therapy (SRT) and chaperone therapy [8]. Research on gene therapy is ongoing. The available treatments slow disease progression rather than curing patients, particularly because treatment is often started after organ damage has already occurred [1,3]. Due to the longer life expectancy offered by drug therapy, new complications and issues appear that need to be treated to improve the adult patients' quality of life. One potential way of achieving this is through nutritional therapy, which can be of benefit in certain clinical manifestations of LSDs, such as metabolic alterations, nephropathy or gastrointestinal symptoms. Furthermore, specific nutritional strategies may modulate autophagy, a process that is adversely affected by lysosomal storage dysfunction and contributes to LSD pathogenesis.

The aim of this review is to describe the benefit or utility of nutritional therapy as an adjunct to currently available treatments in adult patients with some of the more prevalent LSDs, based on the available literature and the authors' personal experience. Nutritional recommendations here discussed are mainly intended for adult patients, as nutrition in infancy and children deserves detailed and age-specific guidance.

Gaucher disease

Gaucher disease (GD), the most common LSD, is caused by the deficiency of lysosomal acid beta-glucosidase, most frequently due to autosomal recessive mutations in the *GBA1* gene [9–11]. This deficiency leads to lysosomal accumulation of the substrate glucocerebroside in many tissues, primarily within macrophages, which causes the formation of characteristic storage cells (or Gaucher cells) in many tissues, resulting in organ damage [9,10]. The most common form of GD (type I, approximately 90% of cases) is characterized by the absence of early-onset neurological impairment, while types II and III are termed neuronopathic GD because they are associated with neurological symptoms from a young age [10,12,13]. Symptoms of type I GD, which can occur at any age and with varying degree of severity and progression, include hepatosplenomegaly, cytopenia, skeletal pathology, pulmonary hypertension and growth retardation [10,12].

The heterogeneity of GD requires an individualized approach to treatment; however, ERT or SRT is recommended for all symptomatic patients, and significantly improves or reverses many manifestations of type I GD; these treatments have transformed the disease phenotype and enhanced patient quality of life [9,12,14,15].

Eliglustat, an SRT available as first-line treatment for selected patients with type I GD, is well tolerated; however, it is mandatory to assess concomitant use of medications, herbal supplements and fruits that might affect cytochrome P450, CYP2D6 and CYP3A metabolism and thus alter eliglustat plasma levels [15]. Patients should be advised accordingly, mainly to avoid grapefruit products, pomegranate, carambola (star fruit), bitter orange, liquorice and herbal products [15]. The SRT miglustat (indicated as second-line therapy for some adult patients with type I GD), can cause gastrointestinal disturbances such as diarrhea, flatulence and abdominal pain or discomfort; these adverse events (AEs) can be reduced by restricting patients' intake of disaccharides as detailed in the section on Niemann-Pick disease type C [16–18].

Metabolic alterations associated with GD include hypermetabolism, insulin resistance and dyslipidemia, with markedly reduced high-density lipoprotein (HDL) cholesterolemia and increased triglyceride and apolipoprotein E plasma levels [19–21]. Low HDL cholesterolemia is currently used as an unspecific biomarker for type I GD [22]. However, unlike in the general population, this unfavorable metabolic profile does not appear to increase the risk of atherosclerosis in GD patients [23]. These metabolic alterations can be partially reversed by ERT or SRT [5], and lipid profiles have been shown to normalize by ERT in type I GD patients [24]. With ageing, patients with stable GD due to therapy may develop other cardiovascular risk

factors, such as metabolic syndrome; these factors are a target for dietary and lifestyle interventions, with aim of preventing comorbidities. However, evaluating the effectiveness of nutritional therapy is complicated by the possible effects of lifestyle and ERT or SRT on metabolic factors, which have not been fully elucidated [5].

Patients with GD have increased resting energy expenditure [25–27], and this may contribute to their growth delay and cause them to be underweight [5]. During treatment with ERT, resting energy expenditure and growth rate almost normalize and patients tend to gain weight [27,28]. However, increases in body weight observed in untreated patients suggest that weight gain may also be associated with dietary habits and a sedentary lifestyle [10,29].

GD is often associated with insulin resistance and increased hepatic glucose production [29–33]; altered insulin signaling due to lysosomal impairment has been demonstrated [33]. These factors are not associated with an increased incidence of type 2 diabetes compared with the general population [29].

Some patients with GD have gastrointestinal symptoms caused by organomegaly, mainly early satiety, abdominal bloating and stomach heaviness [34]. These symptoms can be improved by dividing meals into smaller, more frequent portions and reducing food volume. Cholelithiasis is also frequent, due to biliary secretion of sphingolipids [21].

Skeletal manifestations are a major cause of morbidity in patients with GD [35–38]. ERT and SRT can reduce bone pain and bone crisis, and long-term ERT can also increase bone mineral density (BMD) and prevent bone complications; however, some changes are irreversible [35]. Although there are no studies on the effect of diet or lifestyle on the progression of skeletal damage, patients with GD should receive bone health instructions similar to those given to patients with osteoporosis. These include regular exercise, stopping smoking, limiting alcohol intake, and an adequate intake of vitamin D and dietary calcium [39]. Additionally, malnutrition is a major concern for some patients with GD and this can exacerbate skeletal damage. In these patients, an energy- and protein-rich diet is recommended.

Although there are no specific dietary guidelines for patients with GD, it is important to monitor the nutritional and metabolic status of these patients in order to create a suitable dietary plan which caters to each patient's specific needs.

Pompe disease

Pompe disease (PD), or glycogen-storage disease type II, is an autosomal recessive myopathy in which a deficiency in the acid alpha glucosidase (GAA) enzyme causes an accumulation of lysosomal glycogen and an alteration of the autophagy process [40–43]. Although glycogen accumulates in multiple tissues, the clinical manifestations of the disease mostly affect skeletal and cardiac muscles [42].

The clinical presentation of PD depends on the age of onset. The infantile onset form is more severe and characterized by cardiomyopathy; other symptoms include muscular hypotonia, dysphagia, hepatomegaly and respiratory failure [40]. Without treatment, patients are unlikely to survive beyond one year old [40]. In the late-onset form, symptoms can manifest at any time from infancy to late adulthood and are predominantly related to skeletal muscle dysfunction, which leads to mobility and respiratory difficulties [40].

Although individual responses are variable, ERT improves overall survival, ventilator-free survival, cardiomyopathy and motor development in patients with infantile-onset PD [41,44]. ERT also results in disease stabilization and improved motor and pulmonary function in patients with the late-onset form [41,44].

Additionally, ERT has been shown to improve symptoms that resemble irritable bowel syndrome (IBS), including fecal incontinence and diarrhea, which are experienced by some patients with late-onset PD [45–48].

Dysphagia is common in infantile-onset PD [49] and may also be observed in late-onset PD, suggesting bulbar muscle involvement [50]. Although ERT was shown to improve swallowing difficulties in children with infantile-onset disease, some difficulties were still observed after treatment [49]. Key concerns with dysphagia include malnutrition, dehydration, and airway penetration and aspiration [51]. Management depends on the severity of the condition. Mild-to-moderate dysphagia can be managed with texture-modified diets, which range from soft, easy-to-chew food with small particles to prevent choking, through to smooth pureed food [52]. Patients with liquid-associated dysphagia may benefit from the use of thickening agents that form an easy-to-swallow gel, reducing the risk of aspiration [53]. However, thickened liquids can increase the feeling of satiety and also often have a poor flavor; these factors reduce patients' motivation to consume the gels [53]. Thus it is recommended that the minimum level of thickness needed to maintain swallowing safety is used, and patients must be carefully monitored for dehydration and malnutrition [53]. In patients with severe dysphagia who have a high risk of malnutrition, enteral nutrition is necessary [54]; there are no data available on the gastrostomy technique most suitable for patients with PD.

Low values of bone mineral density (BMD) are common in both patients with infantile and late onset PD [55]. For this reason, vitamin D and calcium supplementation is recommended for all patients with low BMD z-scores [56]. Swallowing dysfunction, causing a reduction of protein intake and increasing endogenous protein breakdown, can adversely affect also bone metabolism [57]. Progressive muscle weakness, exercise intolerance and fatigue reduce physical activity in PD patients, further worsening bone mass loss [58].

Both muscle amino acid turnover and resting energy expenditure are higher in patients with PD than in healthy controls [59]. With the aim of reducing glycogen formation and reducing muscle protein loss, a low-carbohydrate, high-protein diet has been proposed for patients with PD [56]. Small trials and case reports suggest that this diet,

with or without the addition of prescribed aerobic exercise and L-alanine supplementation, improves muscle function or delays muscle deterioration in compliant patients [56–61]. Slonim and coll. reported that a high-protein, low-carbohydrate diet (protein 20–25%, carbohydrates 30–35%, fat 35–40%) associated with exercise therapy, slowed deterioration in muscle function in adult PD patients [60].

Recently, Sechi and coll. [62] investigated in a crossover randomized study the effect of exercise alone, or associated with a high-protein diet (protein 20–25%, carbohydrates 30–35%, fat 35–40%) in 30 PD patients under chronic ERT. Exercise + diet improved the peak of aerobic power, creatine kinase and lactate dehydrogenase plasma levels, and forced expiratory volume respect to control and exercise periods.

As it is difficult for many patients with PD to maintain a high-protein diet, supplementation with L-alanine has been proposed as an alternative way to reduce muscle protein turnover and thus possibly improve muscle function [63]. In one small trial, L-alanine supplementation reduced protein turnover and resting energy expenditure in patients with late-onset PD [63]. A case study has suggested L-alanine may be beneficial in an infant with PD [64]; however, no further data regarding L-alanine supplementation are available.

There is insufficient available evidence to recommend any particular dietary regimen useful for all patients with PD [56]; thus, the most relevant nutritional intervention is to carefully evaluate the individual patient's nutritional status and tailor their diet to meet energy needs.

Acid sphingomyelinase deficiency (Niemann-Pick disease type A,B)

Acid sphingomyelinase deficiency (ASMD), also known as Niemann-Pick disease type A (NPD-A) and type B (NPD-B), is caused by bi-allelic mutations in the sphingomyelin phosphodiesterase1 (*SMPD1*) gene, which encodes lysosomal enzyme acid sphingomyelinase (ASM) [65]. This leads to an accumulation of sphingomyelin (a major component of cell membranes and the myelin sheath) and other lipids in the monocyte-macrophage system [62–64]. NPD-A, the ASMD infantile form, is characterized by rapid, progressive neurodegeneration, and most patients do not survive beyond 3 years of age [66]. Patients fail to achieve developmental milestones and exhibit hepatosplenomegaly and severe hypotonia [66]. NPD-B is the chronic form of the disease; there is little or no neurological involvement and the most frequent presenting symptom is hepatosplenomegaly and pulmonary involvement, with a progressive interstitial lung disease [66]. Dyslipidemia and liver dysfunction is common. Growth and puberty are often delayed [66,67–69].

Although there are no guidelines regarding correct nutrition for patients with ASMD, it is important to assess the nutritional status of these patients. Individualized plans should match patient's diet to their actual requirements, taking resting energy expenditure into account, and may be particularly relevant in late adolescence and adulthood to ensure that nutrition is adequate and to reduce the hyperlipidemia. Therefore lifestyle changes and diet modification have been proposed for the management of some complications of ASMD [65]. It would also be interesting to evaluate the real impact of a low fat diet in these patients. Furthermore, patients undergoing bone marrow or liver or lung transplant need specialized monitoring and advice to reduce the risk of malnutrition.

Niemann-Pick disease type C

Niemann-Pick disease type C (NPD-C) is an autosomal recessive LSD caused by mutations in the *NPC1* gene (95% of families) or the *NPC2* gene [67,70–73]. In patients with NPD-C, impaired intracellular lipid transport leads to an accumulation of non-esterified cholesterol and glycosphingolipids in many tissues, including the brain [67,70–73]. The clinical presentation is extremely heterogeneous, ranging from a rapidly fatal neonatal disease to an adult-onset chronic condition. However, NPD-C is classically a neurovisceral disorder and almost all patients develop a progressive, fatal neurodegenerative disease [74]. The majority of patients will die in late childhood or early adulthood [74]. Characteristic vertical supranuclear gaze palsy is observed in most patients, and splenomegaly and liver involvement are also common. In the United States there is no approved treatment for NPD-C; however, miglustat has been approved in several countries for the treatment of progressive neurological manifestations in patients with NPD-C [67,75]. As mentioned above, miglustat is frequently associated with gastrointestinal disturbances such as diarrhea, flatulence and abdominal pain, and weight loss particularly in the early stages of treatment [16]. These AEs are most likely caused by miglustat inhibiting intestinal disaccharides which leads to impaired absorption [16]. The gastrointestinal tolerability of miglustat can be improved by restricting the patient's intake of disaccharides or carbohydrates, particularly if the dietary modification is initiated before the start of miglustat therapy [16]. Dietary modifications must be individualized; advice should be obtained from a dietitian or gastroenterologist and care must be taken to ensure that the patient maintains an adequate caloric and vitamin intake [16].

Fabry disease

Fabry disease (FD) is an X-linked LSD caused by mutations in the *GLA* gene, which leads to deficient alpha-galactosidase A enzyme activity [76]. This results in progressive accumulation of glycolipids in a wide range of cells, including vascular endothelial cells [76].

Two phenotypes of the disease have been described. Classical FD affects mainly males; symptoms, which include chronic neuropathic pain, angiokeratoma, chronic kidney disease (CKD), cardiovascular dysfunction and subsequent manifestations, and gastrointestinal disturbances,

generally emerge during childhood, are severe and progress rapidly, and lead to multi-organ damage and a shortened life expectancy [76,77]. The later-onset phenotype of Fabry disease is frequent and the typical cardiac symptoms and proteinuria generally emerge in middle-aged or older patients [76].

Because non-specific gastrointestinal symptoms are often one of the presenting signs of FD, patients are often misdiagnosed, or have an extremely long diagnostic delay [78,79]. As early recognition of the disease is crucial for optimal response to ERT [78], it has been suggested that a modified gastrointestinal rating scale, adapted to include questions related to other symptoms of FD, could be a useful diagnostic tool for identifying patients who should be investigated for suspected FD [79].

There are currently two forms of ERT available for treating patients with FD: agalsidase alfa and agalsidase beta [80]. ERT may reduce plasma and urinary glycolipid levels, slow the progression of renal and cardiac impairment and improve peripheral neuropathy and gastrointestinal symptoms in patients with FD [80–84]. A pharmacological chaperone, migalastat, has been approved for the treatment of a subgroup of patients with FD who have mutations that are predicted to be amenable to the drug [76,85]. Migalastat treatment may reduce plasma glycolipid levels, decrease left ventricular mass, slow the progression of renal impairment, reduce neuropathic pain and gastrointestinal symptoms, and improve patients' quality of life [86–89].

Although ERT or migalastat can slow the progression of renal impairment, additional treatment for proteinuric nephropathy will still be required. In terms of dietary therapy, patients with FD should follow similar recommendations to those for other patients with renal dysfunction. There are not enough data to establish a firm guideline regarding protein intake; however, a very low protein diet is not recommended because of the risk of malnutrition and a negative nitrogen balance [90]. Thus, the same protein intake is recommended for patients with nephrotic syndrome as for healthy individuals of the same age and sex [91]; this suggestion may also be followed for patients with FD. However, in patients with CKD, a low- or very low-protein diet, supplemented with keto analogues, could delay the progression of CKD [92]. During hemodialysis, when patients' energy and protein requirements substantially increase, the recommended protein intake is 1.2 g/kg of ideal body weight [93–95], but patients often find it difficult to achieve this recommendation [93]. In patients with nephrotic proteinuria, edema may be reduced by gradually reducing dietary sodium intake to $<$2–3 g/day, while fluid restriction is generally not necessary [86,87,92,90,91,96].

A number of patients with FD experience profound gastrointestinal symptoms, which have a negative impact on their quality of life [97,98]. The symptomology is similar to that in patients with diarrhea-predominant IBS, although feces are devoid of mucus and blood [97]. The most common gastrointestinal symptoms are abdominal pain and diarrhea, and stool frequency in these patients can be as high as 15 per day [74,93–95,78,97–99]. Gastrointestinal symptoms are often exacerbated by eating and patients may also experience early satiety [78,99]. Patients therefore often reduce the amount of food they eat [99], meaning malnutrition is a concern. ERT and migalastat significantly improve gastrointestinal symptoms in patients with FD, but they do not eliminate them [89,97]. Although no studies have specifically investigated dietary therapy to improve gastrointestinal symptoms in patients with FD, the literature suggests treating symptoms in the same way as is recommended for the general population [78]. Patients should have an individualized nutritional plan, created after investigating the correlation of symptoms with specific foods. Small frequent meals may be required, with care taken to ensure adequate nutrient and energy intake [78]. As the symptoms are often similar to those seen in IBS, dietary recommendations may help. These recommendations include monitoring the effects of alcohol, caffeine, spicy foods and dietary fats on symptoms, and decreasing intake if necessary; investigating the impact of increasing dietary fiber; testing for lactose intolerance; and ensuring an adequate intake of non-caffeinated, non-carbonated fluids [100]. Recent studies demonstrated that short-chain fermentable carbohydrates increase small intestinal water content and colonic gas production worsening GI symptoms [101].

There is now also convincing evidence for the clinical efficacy of the low fermentable oligosaccharide, disaccharide, monosaccharide and polyol (FODMAP) diet in patients with IBS [102], so a low FODMAP diet may benefit FD patients.

Mucopolysaccharidoses

The mucopolysaccharidoses (MPS) are caused by a deficiency of enzymes that catalyze the degradation of glycosaminoglycans; there are 11 known enzyme deficiencies which cause MPS [103,104]. MPS II is X-linked and the other forms of MPS are autosomal recessive disorders [99]. The clinical heterogeneity and rarity of MPS means diagnosis is difficult, particularly in patients without cognitive impairment [103]. In addition to intellectual disability observed in several MPS, other possible symptoms include facial dysmorphia, hepatosplenomegaly, skeletal abnormalities and corneal clouding [103], which may aid diagnosis. The introduction of specific ERT has considerably improved the quality of life and life expectancy for patients with some types of MPS [105]. Nutritional monitoring and counselling for patients with MPS are advisable; in a recent evaluation, patients with MPS I, II or VI had inadequate energy and micronutrient intake, and it was suggested that this could impact the course of the disease [106].

MPS type I is caused by a deficiency of the alpha-L-iduronidase enzyme, which leads to an accumulation of two glycosaminoglycans, heparan sulfate and dermatan sulfate, in almost all tissues [104,107]. In the most severe type of MPS I, Hurler's disease, patients exhibit profound

intellectual disability, hepatomegaly and splenomegaly, impaired hearing and vision, and skeletal, respiratory and cardiac complications [99,103,104,107,108]. Patients with severe MPS I, Hurler's disease, generally die within the first decade of life [107]. The clinical presentation of attenuated forms of MPS I (Hurler-Scheie and Scheie syndromes) is far more heterogeneous, with wide variability in age of onset, symptomology, comorbidities and disease course [108]. There is often a significant delay in diagnosis [109], and many of these patients survive into adulthood [108]. HSCT is the first choice of treatment in patients with severe MPS I [8]. When performed early, before the onset of developmental impairment, HSCT can prevent or reverse many symptoms; however, there is a significant risk of morbidity and death with this procedure [8,110,111] and nutritional support is mandatory. ERT with laronidase (recombinant human alpha-L-iduronidase) is also approved for the treatment of patients with MPS I, either as monotherapy or as an adjunct to HSCT, but is unlikely to improve the CNS symptoms of MPS I [112]. In a phase I/II trial, fusing alpha-iduronidase with a monoclonal antibody to allow the enzyme to cross the blood–brain barrier showed little benefit on neurological and cognitive function in patients with MPS I [8], with only marginal improvement in this very intellectually disabled population.

Although studies of nutrition in patients with MPS are scarce, malnutrition is a concern [110], as is the impact of diet and lifestyle choices on patients' cardiovascular and bone health. As with other LSDs, gastrointestinal manifestations of MPS I may be improved by commonly recommended dietary modifications, as described above [108]. Furthermore, studies in MPS I animal models have suggested a fat-rich diet may be beneficial [112,113]. Although the isoflavone genistein may potentially inhibit glycosaminoglycan synthesis and subsequent accumulation and has shown potential in other diseases, supplementation with genistein in a murine model of MPS I produced unexpected AEs, leading the authors to conclude that caution should be exercised while using this approach in humans [114]; clinical trials are ongoing and data are currently insufficient to recommend this treatment.

MPS type III, also known as Sanfilippo syndrome, is a neurodegenerative disorder caused by the failure to degrade heparan sulfate. MPS III is divided into types IIIA, IIIB, IIIC, and IIID, which are distinguished by their genetic alterations. The different types of MPS III have similar manifestations, although the features of MPS IIIA typically appear earlier in life and progress more rapidly. People with MPS III usually live into adolescence or early adulthood.

Coenzyme Q10 (CoQ10) in lysosomal membranes plays a key role in the exchange of electrons where contributes to protons' translocation into the lumen and to the acidification of the intra-lysosomal medium [115]. CoQ10 and pyridoxal phosphate (PLP) deficiency were observed in the majority of patients with MPS III ($n = 9$), leading Authors to conclude that this could partially explain the complex pathophysiology of this disease [116].

Human studies on CoQ10 or antioxidant supplementation in MPS type III are so far lacking. In one *in vitro* study [117], primary skin cultured fibroblasts from five patients with MPS type III were treated with different concentrations of CoQ10 or with an antioxidant cocktail (α-tocopherol, N-acetylcysteine and α-lipoic acid). The treatment with CoQ10 showed a significant increase of residual enzymatic activity in the Sanfilippo B cell lines. Both CoQ10 and antioxidant treatment were able to reduce glycosaminoglycans accumulation in Sanfilippo A and Sanfilippo B cell lines [117]. It was also proposed that CoQ10 and PLP supplementation may be useful as adjunctive therapy, although further investigation in humans is required [116].

There are currently limited data on bone involvement in MPS III, but in a study in 15 patients, BMD was low in 20% of patients and 60% had a vitamin D deficiency [118]. Thus regular checks of vitamin D levels and BMD are recommended to evaluate and possibly address the risk of fractures, especially in older, immobile patients [118]; however, further studies in this area are needed.

In an analysis of serum samples from 25 pediatric patients with MPS III, the lysosomal accumulation of glycosaminoglycans was found to cause deep depression of almost all metabolic pathways, possibly via processes that involve the absorption, transport and biosynthesis of metabolites [119]. Alterations in serum metabolomic profiles could potentially be used as surrogate biomarkers of the response of MPS III to therapy and dietary changes [119]. Although the extent of metabolic impairment means that treatment through diet is unlikely to be beneficial [119], careful management of dietary intake is recommended to reduce the risk of malnutrition. Some patients who experience excessive mucus production may benefit from limiting the amount of sugar and dairy products (including milk) in their diets [120].

Assessment and monitoring of nutritional and metabolic state

Managing the nutritional needs of patients with LSDs is extremely complicated. Patients may be overweight, with the possible development of metabolic syndrome and a consequent worsening of liver disease and increased cardiovascular risk. Conversely, patients may be malnourished, underweight and display growth retardation. Furthermore, therapy such as ERT can modify the metabolic status and needs of patients. Therefore, the nutritional and metabolic status of patients must be assessed regularly in order to rapidly identify and address malnutrition or alterations in glucose or lipid metabolism. This regular monitoring allows the physician to recommend appropriate dietary modification and to assess the efficacy of such changes. Monitoring should include regular measurements of patients' height and weight; the most common sign of malnutrition is rapid involuntary weight loss. Body composition should be assessed using simple clinical methods such as skinfold measurements and bioelectrical impedance analysis or

using the more reliable (albeit more expensive and invasive) total body dual-energy X-ray absorptiometry (DXA). DXA is necessary in particular to monitor bone disease and body composition in patients with LSDs, especially when limited ambulation and malnutrition may worsen bone mass and alter body composition [121]. A food evaluation questionnaire is usually sufficient to estimate a patient's spontaneous nutrient intake, and indirect calorimetry is useful for measuring resting energy expenditure. Alternatively, predictive equations such as Harris-Benedict or Mifflin may be used [122], although these equations were designed for the general population. Disease-specific equations would be ideal but are not yet available for LSDs. Useful laboratory tests for assessing a patient's nutritional status include complete blood count, circulating lymphocyte count, plasma electrolytes, plasma albumin levels, transferrin, vitamins (vitamin D, retinol, vitamin B_{12}, folate), electrolytes, urine nitrogen, iron and ferritin. Serum albumin levels are often reduced in patients with malnutrition and are correlated with the clinical prognosis of many diseases [123]. Additionally, measuring fasting levels of glycaemia and insulinemia and the homeostatic model assessment (HOMA) index to estimate insulin resistance are important in overweight patients, particularly in GD [5]. Patients' lipid profiles must also be monitored and evaluated, especially in ASMD, FD and GD patients. Furthermore, aspartate transaminase and alanine aminotransferase measurements can aid the identification of liver involvement in some LSDs, including metabolic dysfuntion associated fatty liver disease, which is often associated with metabolic syndrome.

Finally, it must be remembered that, like the general population, ageing adult patients with LSDs are subject to common degenerative conditions and atherosclerosis. These conditions can often be prevented or delayed by following mainstream recommendations for the control of cardiovascular and tumor metabolic risk factors with a healthy lifestyle and a balanced diet. Table 1 summarizes our panel recommendations for nutritional management in patients affected by GD, PD, FD, MPS, ASMD, according to current evidences.

Table 1 Recommendations for nutritional management of Gaucher disease, Pompe disease, Fabry disease, mucopolysaccharidoses and acid sphingomyelinase deficiency patients.

Gaucher disease
- Smaller meals to reduce early satiety but without limiting nutrient and energy intake.
- Maintaining adequate intake of vitamin D and dietary calcium.
- Preventing/treating overweight or malnutrition.
- Informing patients regarding bone health with suggestions to quit smoking, regular exercise, and limiting alcohol intake.

Pompe disease
- Mild-to-moderate dysphagia to be managed with texture-modified diets to prevent choking
- Minimum level of thickness needed to maintain swallowing safety to be used.
- Patients must be carefully monitored for dehydration and malnutrition.
- Enteral nutrition may be necessary in patients with severe dysphagia.
- A low-carbohydrate, high-protein may also be used.

ASMD (NPD A,B)
- Lifestyle changes and reduced lipid intake may be beneficial in the management of adolescents and adults ASMD B (NPB) with hyperlipidemia
- Manage bone health with suggestions to quit smoking, regular exercise, appropriate intake of calcium and vitamin D and limiting alcohol intake

Niemann-Pick disease type C
- Restrict intake of disaccharides or carbohydrates before initiating miglustat therapy
- Evaluate and treat vitamin deficiencies due to possible malabsorption with miglustat.

Fabry disease
- Smaller meals to reduce early satiety but without limiting nutrient and energy intake.
- Individualized nutritional plan depending on symptoms and renal function; a low FODMAP diet may be beneficial.
- Monitor the intake of alcohol, caffeine, spicy foods, dietary fats, dietary fiber, and dairy products (for lactose intolerant patients), and limit them, if necessary.
- In patients with CKD, a low-protein diet, may delay the progression of CKD.
- In patients with nephrotic proteinuria, reduction of dietary sodium intake to <2–3 g/day (sodium chloride 5–7 g/day) generally without fluid restriction is recommended

Mucopolysaccharidosis
- Nutritional monitoring and counselling of patients is recommended.
- Gastrointestinal manifestations may be improved by dietary modifications (as above).
- Careful management of dietary intake to reduce the risk of malnutrition.
- Regular checks of vitamin D levels and BMD are recommended.

BMD, bone mineral density; CKD, chronic kidney disease; FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide and polyol.

Future prospects: dietary modulation of autophagy

Lysosomes can be considered the cell's 'metabolic brain' because they act as energy-state sensors and can activate required regulation mechanisms. This activity is closely connected to kinase systems that regulate cell anabolism and catabolism (mammalian target of rapamycin complex 1 [mTOR] and AMP kinase) and contribute to the metabolic alterations seen in LSDs.

A common feature in LSDs is damage to the autophagic process [4,124], as lysosomes are involved in both macro- and microautophagy. Impaired macroautophagy causes accumulation of aged, damaged mitochondria and other cell elements [125]. Oxidative stress caused by defective mitochondria leads to inflammation and an accumulation of modified protein aggregates [125], as has been observed in other diseases such as Alzheimer's, Parkinson's and Huntington's disease [4,126]. Because autophagy is sensitive to the intake of energy and nutrients, it may be possible to modulate it through pharmacological agents and diet. Ketone bodies activate autophagy and reduce inflammatory processes, via the activation of AMP kinase [127,128]: a ketogenic diet has been investigated as a possible method for interfering with the ageing

process and it is a useful treatment to help manage refractory epilepsy [129]. In rats, a ketogenic diet reduced the formation of free radicals and improved mitochondrial efficiency [130]. Nevertheless, the efficacy of a ketogenic diet has not yet been demonstrated in LSD patients.

A murine model of PD showed that diet modulated the autophagy process by acting on mTOR kinase complex [131], a complex located on the surface of lysosomes that stimulates cell growth and protein synthesis while inhibiting autophagy, and is activated by amino acids, insulin and growth factors, but inhibited by fasting [132]. In the Pompe mouse model [131], mTOR appeared dysregulated, leading to reduced protein synthesis, increased proteolysis and muscle damage. Supplementation with amino acid L-arginine normalized mTOR activity in this PD murine model [131], but has never been evaluated in LSD patients. Additionally, fasting and caloric restriction may upregulate autophagy, as seen in animal models [126], but have not been investigated in humans. However, this approach may not be advisable in underweight patients with LSDs for obvious reasons and has never been tested.

Experimental dietary intervention in LSDs

Other interesting experimental dietary interventions in patients with LSDs, such as Coenzyme Q10 and pyridoxal phosphate supplementation in MPS III, L-alanine supplementation in PD, genistein or a fat-rich diet in MPS I need further investigation and cannot be recommended yet.

Conclusions

Despite the improvement in clinical outcome of many LSDs by specific therapies, numerous symptoms still persist. The clinical manifestations of LSDs are often sensitive to dietary modification. Therefore, metabolic and nutritional assessments and monitoring are advisable for all patients with LSDs, with the aim of preventing comorbidities, excessive weight gain or malnutrition and their related complications. Nutritional therapy is also very important to ensure proper growth and to achieve peak bone mass in young patients with GD, ASMD, and MPS, and to manage dyslipidemia in FD and ASMD adults. Alterations in the autophagy process, a pathogenic mechanism in LSDs, may be potentially sensitive to dietary manipulation, but clinical studies are required to assess the potential of nutritional interventions in modulating lysosomal activity.

Author contributions

Francesca Carubbi contributed to the study design and web search, reviewed the current literature and wrote some drafts, actively participated in the preparation of the manuscript and read and approved drafts. Antonio Barbato contributed to the study design and web search, reviewed the current literature and wrote some drafts, actively participated in the preparation of the manuscript and read and approved drafts. Alberto B Burlina contributed to the study design and web search, actively participated in the preparation of the manuscript and read and approved drafts. Francesco Francini-Pesenti coordinated the study, contributed to the study design and web search, reviewed the current literature and wrote some drafts, actively participated in the preparation of the manuscript and read and approved drafts. Renzo Mignani contributed to the study design and web search, reviewed the current literature and wrote and approved some drafts of the manuscript. Elena Pegoraro contributed to the study design and web search, actively participated in the preparation of the manuscript and read and approved drafts. Linda Landini contributed drafting the manuscript and critically revised the various drafts of the manuscript and approved the final version before submission. Gianluca De Danieli contributed to the discussion of the topics, reviewed the various drafts of the manuscript and approved the final version before submission. Stefano Bruni contributed to the discussion of the topics, reviewed the various drafts of the manuscript and approved the final version before submission. Pasquale Strazzullo contributed to the study design and web search, actively participated in the preparation of the manuscript and read and approved drafts.

Declaration of competing interest

Francesca Carubbi received honoraria for lectures, advisory board and meetings from Amgen, Sanofi, Shire and Amicus. Francesco Francini-Pesenti received honoraria for advisory boards and meetings from Sanofi. Elena Pegoraro has been a scientific advisory board or data safety monitoring board for PTC Therapeutics, Sarepta Therapeutics, Santhera Pharmaceuticals, Genzyme and Roche, received funding for travel and educational support from Genzyme and PTC Pharmaceuticals, received funding for travel support from Santhera and is receiving grant support from Santhera. Antonio Barbato received honoraria for lectures, advisory boards and meetings from Sanofi Genzyme and Takeda Shire. Renzo Mignani received honoraria for lectures, advisory boards and meetings from Sanofi-Genzyme, TakedaShire, Otsuka Pharmaceutical, and Amicus-Therapeutics. Alberto B Burlina has received a speaker honoraria and travel support from Sanofi Genzyme, Actelion, Takeda, Nutricia, Danone, PIAM Medifood, Biomarin. Linda Landini has been an employee of Sanofi Genzyme. Gianluca De Danieli is an employee of Sanofi Genzyme. Stefano Bruni has been an employee of Sanofi Genzyme. Pasquale Strazzullo received honoraria and travel support as speaker and/or advisory board from Sanofi Genzyme and Takeda Shire.

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