IWGGD The International Working Group on Gaucher Disease

Guideline	**Gaucher type 1 in adults: Nutrition and healthy lifestyle**
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Overview	Since the existence of treatments for Gaucher Disease (GD), patients have improved overall survival and quality of life. Nutritional and healthy lifestyle issues are important in adult patients with GD with respect to cardiovascular risk, liver diseases and bone health. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence and formulate recommendations (https://www.gradeworkinggroup.org).
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Healthy lifestyle to reduce cardiovascular risk and liver disease

Introduction

With aging, patients with stable GD may develop common cardiovascular risk factors, such as hypertension and metabolic syndrome; these factors are a target for dietary and lifestyle interventions intending to prevent comorbidities. However, evaluating the effectiveness of nutritional therapy is complicated by the possible overlapping effects of lifestyle and enzyme replacement therapy (ERT) or substrate reduction therapy (SRT) on metabolic factors (1).

GD is characterized by hypermetabolism, insulin resistance, and dyslipidemia, with markedly reduced serum high-density lipoprotein (HDL) cholesterol and increased triglycerides. Resting energy expenditure and growth rate almost normalizes during GD-related treatment, and patients tend to gain weight. However, increased body weight observed in untreated patients with aging suggests that weight gain and metabolic syndrome development may also be associated with dietary habits and a sedentary lifestyle (2). Celiac disease has been reported in association with GD, like other autoimmune disorders. Cholelithiasis is frequent in patients with GD due to the biliary secretion of sphingolipids.

Evidence

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. Low HDL cholesterolemia is commonly used as a biomarker for type I GD. However, unlike in the general population, this unfavorable lipid profile did not appear to increase the risk of atherosclerosis in patients with GD (3).

Type 1 GD is often associated with insulin resistance and increased hepatic glucose production. Despite demonstrating altered insulin signaling due to lysosomal impairment, no increased incidence of type 2 diabetes compared with the general population was observed (4). These metabolic alterations can be partially reversed by ERT or SRT. Lipid profiles have been shown to normalize by ERT in patients with type I GD. Nevertheless, adult patients with GD may develop overweight, obesity, metabolic syndrome, secondarily type 2 diabetes, and cardiovascular diseases, which are still a leading cause of death for patients with GD. A healthy lifestyle should be recommended for all patients. All scientific societies and the World Health Organization (WHO) recommend a balanced diet and an active lifestyle for healthy aging. A reduction in animal products, saturated fats, hydrogenated fatty acids, and ultra-processed food has been shown to reduce all-cause mortality, cardiovascular morbidity and mortality, diabetes, neurodegenerative disorders such as Parkinson's and Alzheimer's, and most cancers.

Recommendations:

As for the general population, the panel recommends that patients with GD keep a healthy lifestyle with regular exercise and a balanced diet to reduce the risk for cardiovascular disease.

The panel considers as a good practice to include the patients' diet, exercise, and lifestyle-related data as part of the history taken during each GD clinic visit.

Details:

- **Dietary patterns** beneficial for cardiovascular health are predominantly plant-based, consisting of high consumption of whole grains, vegetables, fruits, legumes, nuts, and seeds; moderate consumption of fish, lean poultry, and eggs; and limited consumption of red and processed meat, sweets, salt, energy-dense food, alcohol, and sugar-sweetened beverages. The Mediterranean Diet (with olive oil and nuts), the Portfolio Diet, the fish-vegetarian diet, and the Dietary Approach to Stop Hypertension (DASH) diet are well-known examples of healthy dietary patterns. Although the benefit of these dietary patterns was not specifically investigated in adults with GD, we would see no detriment in having similar recommendations as for the general population.
- **Everyday tips**: increase vegetables, fruits, and berries, fish, nuts, and seeds; exchange refined cereals with whole grain cereals; replace butter and spreads with vegetable oils, exchange high-saturated dairy with low-fat dairy; limit red and processed meat, alcohol, sweet food and beverages, salt, and salty snacks.
- **Nutritional supplements** usually are unnecessary or recommended: a balanced, varied diet can provide all minerals, nutrients, and trace elements needed. Many scientific societies warn against supplements, especially for cancer prevention: vitamins A and E used as antioxidant agents can be liver toxic when added at a high dose. Dietary sources of **vitamin A** are liver, sweet potatoes, carrots, milk, and egg yolks. Vegetable oils (wheat germ oil), avocados, nuts, seeds, and whole grains are a source of **vitamin E**. **Vitamin C** is abundant in oranges, blackcurrants, kiwifruit, mangoes, broccoli, spinach, cruciferous veggies, and strawberries.
- **Natural antioxidants and antiaging agents** from organic sources are preferred and recommended, such as polyphenols of olive oil and oregano; lycopene of tomatoes and watermelon; allium sulfur compounds of leeks, onions, and garlic; anthocyanins of eggplant, grapes, and berries; beta-carotene of pumpkin, mangoes, apricots, carrots, spinach, and parsley; catechins of tea. Seafood, lean meat, whole cereals, milk, and nuts provide copper, selenium, manganese, and zinc; green tea, citrus fruits, red wine, onion, and apples provide flavonoids; pumpkin and mangoes are a font of cryptoxanthins; cruciferous vegetables such as broccoli, cabbage and cauliflower are a source of indoles; soybeans, tofu, lentils, peas, and milk are rich in isoflavonoids; lutein is abundant in green, leafy vegetables like spinach and in corn (5). A well-balanced diet, which includes dietary antioxidants from whole foods, is best. Although the benefit of these dietary patterns was not specifically investigated in adults with GD, we would see no detriment in having similar recommendations as for the general population.
- **Novel diets,** such as “time-restricted eating diets,” “intermittent fasting,” and ketogenic diets, have not been studied in patients with GD. In obese people, short-term evidence is available on their effectiveness in reducing body weight and glycemia but not in reducing cardiovascular and cancer risk in the long term. Keto diets are unbalanced, lack fiber and calcium, and increase blood cholesterol levels. There are observations that in the long run, the ketogenic diet can cause insulin resistance, pre-diabetes, and diabetes (6). Their claimed efficacy against

neurodegenerative disorders and aging is mainly indirect. These special diets should not be recommended; their adverse metabolic, renal, and skeletal effects have been shown. In specific patients, therapeutic diets (such as keto diets for refractory epilepsy) have to be carefully managed and followed up by nutritional therapy experts in collaboration with neurologists experienced in the field of neurometabolomics.

- **Regular exercise** can alleviate or prevent diabetes, hypertension, overweight and obesity, cancer, heart attacks, and overall cardiovascular risk and improve the condition of the osteoarticular system. Reducing sedentary time and increasing physical activity is a relevant intervention to improve public health. Exercise duration and goals have arbitrarily been set: walking about 30-40 min per day (150 min per week), practicing sports and attending gyms, and taking stairs instead of elevators are all considered effective cardiovascular risk preventive measures. Aerobic and anaerobic exercise are both beneficial in preventing or reducing overweight and obesity. Exercise may prevent fracture risk and osteoporosis and favor psychological well-being and quality of life.

The panel suggests regular annual checking of vitamin B12 and folic acid in patients with GD to guide supplementation when needed.

Details:

- Low **vitamin B 12** has been reported in Patients with GD (7), depending on individual dietary intake and drug use. Regular annual checking of plasma vitamin status may guide supplementation when needed.
- **Folate** intake may be low in people with vegetarian diets or unbalanced diets and must be supplemented, particularly before and during pregnancy.

Bone health

Introduction

Skeletal manifestations constitute a significant cause of morbidity in patients with GD (8). It was shown that bone changes might cause chronic pain, limit the independence of patients with GD and significantly reduce their quality of life. Almost 20% of patients have mobility reduced by joint lesions, including bone deformation, osteopenia/ osteoporosis, aseptic necrosis, or pathological fractures. ERT and SRT can reduce bone pain and bone crisis, and long-term treatment can also increase bone mineral density (BMD) and prevent bone complications; however, some changes are irreversible, and arthroplasty may be needed.

Evidence

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 osteopenia or osteoporosis. Nutritional therapy is very important to ensure proper growth and achieve peak bone mass in young patients with GD.

Recommendations:

The panel suggests that patients with GD receive bone health instructions as part of their regular visit to the Gaucher clinic.
Patients with osteoporosis may benefit from a consultation with osteoporosis experts to evaluate for non-GD-related causes and intervention options.

Details:

- It is advised for patients with GD to exercise regularly, avoid smoking, and limit alcohol intake, as these factors are important regulators of bone turnover.
- An adequate intake of **vitamin D** and dietary **calcium** should be provided (9). Drinking water (at least 1-2 liter a day) and regularly eating legumes, nuts, and fresh dairy products, which are rich in calcium, are recommended daily. Low-dose calcium supplements are usually needed only during pregnancy, lactation, and in menopausal women if their diet does not provide the required daily allowance of 1-2 grams.

The panel suggests regular annual checking of vitamin DOH blood levels in patients with GD to guide supplementation when needed.

- Vitamin D supplements may be required, depending on the sex, age, race, latitude light exposure, and dietary intake of individual patients. Vitamin D3 deficiency promotes bone changes. As high blood levels of vitamin D may be toxic, minor refracted weekly supplementation is preferred to a high monthly supplement. Most GD clinics assess vitamin D levels routinely, usually once a year. In case of significant level deficiencies and intensive supplementation, it may be necessary to follow up after 3-6 months. Some GD clinics evaluate vitamin D levels in specific cases, not routinely, particularly in wintertime and in patients with an unbalanced diet or insufficient hydration and outdoor life.
- Vitamin D and calcium supplements at physiological doses are recommended as a first-line treatment for patients with osteoporosis on diphosphonate therapy (9).

Dietary advice for patients on GD-specific treatments

Introduction

Eliglustat, an SRT available as first-line treatment for selected adult patients with type I GD, is usually well tolerated; however, it is mandatory to assess the concomitant use of medications, herbal supplements, and fruits that might affect cytochrome P450 (CYP) 2D6 and CYP3A metabolism and thus alter eliglustat plasma levels (10). The SRT miglustat (indicated as second-line therapy for some adult patients with type I GD) is frequently associated with gastrointestinal disturbances such as diarrhea, flatulence, abdominal pain or discomfort, and weight loss (11).

Evidence

Guidelines recommend which medications and food could interfere with eliglustat treatment (10). Many patients do not tolerate miglustat for gastrointestinal adverse effects; these adverse events (AEs) can be reduced by limiting patients' intake of disaccharides and a specific diet. There are no particular diet recommendations and dietary restrictions when using ERT

Recommendations

The panel recommends following the guidelines of which medications and food could interfere with eliglustat treatment.

- Eliglustat-treated patients should be advised to restrict or avoid grapefruit products, pomegranate, carambola (star fruit), bitter orange, licorice, and herbal products (10). Herbal supplements and over-the-counter self-medications may interfere with eliglustat metabolism and should be reported to the treating physicians for advice. Regular information to patients regarding compatible medications and supplements is recommended.

For patients treated with miglustat, the panel suggests monitoring for abdominal symptoms and vitamin deficiencies to provide dietary advice when needed.

- Miglustat-treated patients should restrict their intake of disaccharides or carbohydrates before initiating therapy. Bloating and diarrhea may be frequent complications during miglustat treatment. Monitoring the effects of spicy foods and dietary fats on symptoms may help to find the best-tolerated diet. Testing for lactose intolerance is advised. Ensuring an adequate intake of non-caffeinated, non-carbonated fluids may help. Short-chain fermentable carbohydrates increase small intestinal water content and colonic gas production, worsening GI symptoms. In some instances, the low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet may benefit patients.

Dietary benefits on unspecific patients' symptoms

Introduction

Some patients with GD have **gastrointestinal symptoms** caused by organomegaly, mainly early satiety, abdominal bloating, and stomach heaviness. These symptoms can be improved by dividing meals into smaller, more frequent portions and reducing food volume at each meal.

Celiac disease should be suspected and evaluated in case of persistent anemia, asthenia, abdominal pain, iron deficiency, or osteopenia with arthralgias. If so, a gluten-free diet can alleviate those symptoms and is the appropriate treatment. Non-celiac **gluten sensitivity** may be diagnosed upon exclusion of celiac disease in those patients who alleviate their symptoms and parameters with a gluten-free diet.

When available, food intolerances should be assessed with specific tests (such as lactose intolerance) or with challenge and re-challenge tests with the suspected food to ensure specific dietary restrictions are needed. Unnecessary dietary restrictions can be harmful to the patient in the long run and should be avoided.

Cholelithiasis is also frequent in patients with GD: an abdominal ultrasound is recommended once a year and in case of pain, gastralgia and bloating are frequently

occurring. Gallstones are strongly related to high-fat, low-fiber diets. Large, fatty meals, as a large caloric load is the most likely trigger for biliary colic symptoms.

Nutritional evaluation

Introduction

Patients with GD have increased resting energy expenditure, which may contribute to their growth delay and cause them to be underweight (2). Therapies normalize children with GD growth and positively affect metabolism in all patients with GD. However, the nutritional status evaluation is helpful to the timely detection of malnutrition risk, selective malnutrition, and overweight or underweight. Additionally, malnutrition can exacerbate skeletal damage.

Evidence

Although there are no specific dietary guidelines for patients with GD, it is important to monitor the nutritional and metabolic status to create a suitable dietary plan which caters to each patient's specific needs. In malnourished patients, an energy- and protein-rich diet is recommended. Nutritional evaluation is mandatory before a specific, personalized nutritional therapy is applied and should be repeated and monitored to evaluate nutritional treatment efficacy.

Recommendations:

The panel recommends monitoring **nutritional status** on a regular basis, including measurements of patients' height (in children), weight, body composition, and laboratory testing.

Details

- The most common sign of malnutrition is rapid involuntary weight loss. In children, malnutrition may manifest as a slowdown in the growth rate. In adult patients, the height reduction may signify vertebral collapse and skeletal complications.
- **Body composition** can 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), which is useful to monitor bone disease and body composition at the same time in adult patients with GD.
- 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 D3, vitamin B12, folate), calcium, and in clinically justified situations, PTH and phosphates levels, 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.
- Measuring fasting levels of glycemia and insulinemia and the homeostatic model assessment (HOMA) index to estimate insulin resistance is important in overweight patients with GD. Patients' lipid profiles should also be monitored. Serum aspartate and alanine transaminase measurements can aid the identification of liver

involvement, including metabolic dysfunction associated with fatty liver disease (MAFLD), which is often associated with metabolic syndrome.

Future LSDs research developments

Specific nutritional strategies may modulate autophagy, a process that is adversely affected by lysosomal storage dysfunction and contributes to GD pathogenesis. However, studies in humans are not available yet.

Autophagy is sensitive to the intake of energy and nutrients. Therefore, 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. In vitro and animal models, the dietary modulation of the autophagic flux is under investigation. Fasting and caloric restriction may upregulate autophagy, as seen in animal models, but have not been investigated in humans. This approach, of course, may not be advisable in underweight or malnourished patients.

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