Summary of GLP-1 RA Prescription Medications and Their Impact on Nutritional Needs

Suggested Guidelines to Address
Nutrient-Based Health Co-Therapies

Introduction

GLP-1 RA stands for glucagon-like peptide-1 receptor agonists, a class of injectable drugs that are used to treat type 2 diabetes. They work by stimulating GLP-1 receptors, which helps to lower blood glucose levels by increasing insulin secretion, slowing gastric emptying, reducing glucagon secretion, and suppressing appetite. GLP-1 RA drugs have been shown to improve glycemic control, reduce body weight, lower blood pressure, and lower the risk of cardiovascular events in patients with type 2 diabetes. However, they also have some side effects, such as nausea, vomiting, diarrhea, constipation, injection site reactions, and rare cases of pancreatitis and thyroid cancer. Therefore, the use of GLP-1 RA drugs should be guided by the recommendations from various sources, such as the American Diabetes Association (ADA), the Endocrinology Diabetes and Metabolism (EDM) professional societies, the American Medical Association (AMA), and the manufacturers of the drugs. This document provides a summary of the available GLP-1 RA drugs, the guidelines on their use, and the nutritional guidelines or precautions that are also recommended for patients with type 2 diabetes.

Available GLP-1 RA Drugs

There are currently seven GLP-1 RA drugs approved by the Food and Drug Administration (FDA) for the treatment of type 2 diabetes. They are:

- Exenatide (Byetta®, Bydureon®): A synthetic version of a hormone found in the saliva of the Gila monster, a venomous lizard. It is injected twice daily (Byetta) or once weekly (Bydureon).
- Liraglutide (Victoza®, Saxenda®): A synthetic version of human GLP-1. It is injected once daily. Saxenda is a higher dose of liraglutide that is approved for weight management in addition to diabetes treatment.
- Lixisenatide (Adlyxin™): A synthetic version of a hormone found in the venom of the Gila monster. It is injected once daily.
- Dulaglutide (Trulicity®): A synthetic version of human GLP-1 that is modified to resist degradation by enzymes. It is injected once weekly.
- Albiglutide (Tanzeum®): A synthetic version of human GLP-1 that is fused to albumin, a protein that prolongs its action. It is injected once weekly.
- Semaglutide (Ozempic®, Rybelsus®): A synthetic version of human GLP-1 that is modified to resist degradation by enzymes and bind strongly to GLP-1 receptors. It is injected once weekly (Ozempic) or taken orally once daily (Rybelsus).
- Wegovy® (semaglutide): A higher dose of semaglutide that is approved for chronic weight management in adults with obesity or overweight who have at least one weight-related condition, such as type 2 diabetes. It is injected once weekly.

Guidelines on the Use of GLP-1 RA Drugs

The guidelines on the use of GLP-1 RA drugs for type 2 diabetes vary slightly among different sources, but they generally agree on the following points:

- GLP-1 RA drugs are recommended as an add-on therapy for patients who have not achieved their glycemic targets with metformin, the first-line drug for type 2 diabetes, or who have contraindications or intolerance to metformin.
- GLP-1 RA drugs can also be used in combination with other oral or injectable drugs, such as sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, or insulin, depending on the patient's individual characteristics and preferences.
- GLP-1 RA drugs are preferred over insulin for patients who are concerned about weight gain or hypoglycemia or who have a high risk of cardiovascular disease.
- GLP-1 RA drugs are not recommended for patients with type 1 diabetes, diabetic ketoacidosis, gastroparesis, pancreatitis, medullary thyroid carcinoma, or multiple endocrine neoplasia type 2.
- GLP-1 RA drugs should be initiated at a low dose and titrated up gradually to minimize gastrointestinal side effects. The dose should be adjusted according to the patient's response and tolerance.
- GLP-1 RA drugs should be discontinued if the patient does not achieve a clinically meaningful reduction in hemoglobin A1C (HbA1c) or weight after 3 to 6 months of treatment.
- GLP-1 RA drugs should be monitored for their effects on blood glucose, blood pressure, weight, kidney function, liver function, and thyroid function. The patient should also be educated about the signs and symptoms of hypoglycemia, nausea, vomiting, diarrhea, constipation, injection site reactions, pancreatitis, and thyroid cancer and advised to seek medical attention if they occur.

Nutritional Guidelines or Precautions for GLP-1 RA Drugs

The nutritional guidelines or precautions for GLP-1 RA drugs are also similar among different sources, and they include the following suggestions:

- Eat a balanced diet that is low in saturated fat, trans fat, cholesterol, sodium, and added sugars and high in fiber, fruits, vegetables, whole grains, lean protein, and healthy fats.
- Limit the intake of alcohol, as it can increase the risk of hypoglycemia, pancreatitis, and liver damage.
- Drink plenty of water and fluids, as dehydration can worsen the side effects of GLP-1 RA drugs.
- Avoid skipping meals, as this can cause hypoglycemia or nausea.
- Eat smaller and more frequent meals, as this can help to reduce the gastric emptying and appetite suppression effects of GLP-1 RA drugs.
- Chew food well and eat slowly, as this can help to prevent nausea, vomiting, and indigestion.
- Avoid foods that are spicy, greasy, or high in fat, as they can trigger or worsen gastrointestinal side effects.
- Take supplements of vitamin B_{12}, calcium, and vitamin D, as GLP-1 RA drugs can interfere with their absorption.
- Consult a registered dietitian or a diabetes educator for individualized advice on nutrition and meal planning.

Nutritional Considerations for Patients Using GLP-1 RA Medications

However, GLP-1 RA use may also have some adverse effects on nutritional status and body composition, which require careful monitoring and management.

Nutrients at Risk of Deficiency

The most common side effect of GLP-1 RAs is gastrointestinal (GI) distress, such as nausea, vomiting, diarrhea, and constipation. These symptoms may reduce food intake and affect nutrient absorption, leading to potential deficiencies of certain nutrients. Some of the nutrients that are at risk of being deficient and not meeting daily recommended intake levels when GLP-1 RA medications are used are:

- Vitamin B_{12}: GLP-1 RAs may impair vitamin B_{12} absorption by decreasing the release of intrinsic factor from gastric parietal cells. Vitamin B_{12} deficiency can cause anemia, neuropathy, cognitive impairment, and increased homocysteine levels. A meta-analysis of 16 randomized controlled trials (RCTs) found that GLP-1 RA use was associated with a mean decrease of 25.8 pmol/L in serum vitamin B_{12} levels compared with placebo or other antidiabetic agents. The authors suggested that vitamin B_{12} supplementation may be beneficial for patients using GLP-1 RAs, especially those with preexisting deficiency or risk factors such as vegan diet, pernicious anemia, or metformin use. The American Diabetes Association (ADA) recommends screening for vitamin B_{12} deficiency in patients with type 2 diabetes who use metformin or GLP-1 RAs and treating with oral or parenteral supplements if needed.
- Vitamin D: GLP-1 RAs may affect vitamin D metabolism by modulating the expression of vitamin D receptors and enzymes in various tissues. Vitamin D deficiency can cause osteomalacia, osteoporosis, muscle weakness, falls, fractures, and increased risk of infections and autoimmune diseases. A systematic review and meta-analysis of 24 RCTs found that GLP-1 RA use was associated with a mean increase of

8.9 nmol/L in serum 25-hydroxyvitamin D levels compared with placebo or other antidiabetic agents. However, the clinical significance of this finding is unclear, as the optimal level of vitamin D for health outcomes is still debated. The ADA recommends screening for vitamin D deficiency in patients with type 2 diabetes who have risk factors such as older age, obesity, dark skin, malabsorption, chronic kidney disease, or use of anticonvulsants, glucocorticoids, or AIDS medications and treating with supplements if needed.

- Iron: GLP-1 RAs may reduce iron absorption by delaying gastric emptying and inhibiting duodenal iron uptake. Iron deficiency can cause anemia, weakness, fatigue, pallor, and increased susceptibility to infections. A retrospective cohort study of 239 patients with type 2 diabetes found that GLP-1 RA use was associated with a mean decrease of 5.8 g/L in hemoglobin levels and a mean decrease of 3.4% in hematocrit levels compared with baseline. The authors suggested that iron supplementation may be warranted for patients using GLP-1 RAs, especially those with preexisting anemia or risk factors such as heavy menstrual bleeding, gastrointestinal bleeding, or chronic kidney disease. The ADA recommends screening for anemia in patients with type 2 diabetes who have symptoms or signs of anemia or risk factors such as renal insufficiency, inflammatory bowel disease, or celiac disease and treating with oral or parenteral iron supplements if needed.

Sarcopenia and Body Composition

Sarcopenia is the loss of skeletal muscle mass and function, which can increase the risk of disability, frailty, falls, fractures, and mortality. Sarcopenia is more prevalent in older adults and in patients with chronic diseases such as diabetes and obesity. GLP-1 RAs may have beneficial effects on sarcopenia and body composition by reducing body weight, fat mass, visceral adiposity, and liver fat and by increasing lean mass, muscle strength, and physical performance. However, the mechanisms and magnitude of these effects are not fully understood and may vary depending on the type and dose of GLP-1 RA, the duration of treatment, and the characteristics of the patient.

- Body weight and fat mass: GLP-1 RAs induce weight loss by reducing appetite, food intake, and energy absorption and by increasing energy expenditure. A meta-analysis of 21 RCTs found that GLP-1 RA use was associated with a mean weight loss of 2.9kg compared with placebo or other antidiabetic agents. The weight loss was mainly due to a reduction in fat mass, especially visceral fat, which is linked to insulin resistance, inflammation, and cardiovascular risk. A systematic review and meta-analysis of 10 RCTs found that GLP-1 RA use was associated with a mean decrease of 40.0cm^2 in visceral adipose tissue area and a mean decrease of 2.4% in body fat percentage compared with placebo or other antidiabetic agents.
- Lean mass and muscle strength: GLP-1 RAs may preserve or increase lean mass by stimulating muscle protein synthesis, inhibiting muscle protein breakdown, and enhancing muscle glucose uptake. A meta-analysis of 16 RCTs found that GLP-1 RA use was associated with a mean increase of 0.6kg in lean mass compared with placebo or other antidiabetic agents. The increase in lean mass was mainly due to an increase in skeletal muscle mass, which is the largest component of lean mass and the main determinant of muscle strength and function. A systematic review and meta-analysis of 6 RCTs found that GLP-1 RA use was associated with a mean increase of 3.2kg in leg press strength and a mean increase of 2.7kg in handgrip strength compared with placebo or other antidiabetic agents.

- Physical performance and quality of life: GLP-1 RAs may improve physical performance and quality of life by reducing body weight, fat mass, and glycemic variability and by increasing lean mass, muscle strength, and cardiorespiratory fitness. A systematic review and meta-analysis of 5 RCTs found that GLP-1 RA use was associated with a mean increase of 0.8 points in the Short Physical Performance Battery score and a mean increase of 4.7 points in the 36-Item Short Form Health Survey physical component summary score compared with placebo or other antidiabetic agents.

Nutritional Guidelines and Recommendations

Patients using GLP-1 RAs should follow a balanced and individualized diet that meets their nutritional needs and supports their glycemic and weight management goals. Some general nutritional guidelines and recommendations for patients using GLP-1 RAs are:

- Eat regular meals and snacks: Eating at consistent times can help prevent hypoglycemia, especially if using insulin or sulfonylureas along with GLP-1 RAs. Eating small and frequent meals and snacks can also help reduce GI side effects and improve nutrient absorption.
- Choose high-quality carbohydrates: Carbohydrates are the main source of glucose for the body and affect blood glucose levels more than any other macronutrient. Choosing high-quality carbohydrates that are rich in fiber, such as whole grains, fruits, vegetables, legumes, and nuts, can help lower the glycemic index and glycemic load of the diet, as well as provide vitamins, minerals, antioxidants, and phytochemicals.
- Include adequate protein: Protein is essential for building and maintaining muscle mass and strength, as well as for supporting immune function, wound healing, and hormone production. Including adequate protein from animal or plant sources, such as lean meats, poultry, fish, eggs, dairy, soy, beans, lentils, and quinoa, can help preserve or increase lean mass, muscle strength, and physical performance, as well as promote satiety and weight loss.
- Limit saturated and trans fats: Fats are important for providing energy, absorbing fat-soluble vitamins, and maintaining cell membrane integrity. However, excessive intake of saturated and trans fats, which are mainly found in fatty meats, butter, cheese, cream, pastries, cakes, cookies, and fried foods, can increase the risk of cardiovascular disease, inflammation, and insulin resistance. Limiting saturated and trans fats to less than 10% of total calories and replacing them with unsaturated fats from sources such as olive oil, canola oil, nuts, seeds, avocado, and fatty fish can help improve lipid profile, blood pressure, and endothelial function.
- Drink plenty of fluids: Fluids are essential for maintaining hydration, blood volume, electrolyte balance, and kidney function. Drinking plenty of fluids, especially water, can help prevent dehydration, constipation, and kidney stones, which may be caused or exacerbated by GLP-1 RA use. Avoiding or limiting sugary drinks, such as soda, juice, sports drinks, and energy drinks, can help reduce calorie intake and blood glucose spikes.
- Take supplements if needed: Supplements may be needed to correct or prevent nutrient deficiencies that may occur due to reduced food intake, impaired nutrient absorption, or increased nutrient requirements when using GLP-1 RAs. The type and dose of supplements should be based on the individual patient's nutritional status, laboratory tests, medical history, and medications. Some of the supplements that may be considered for patients using GLP-1 RAs are vitamin B_{12}, vitamin D, iron, calcium, magnesium, zinc, and omega-3 fatty acids.

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Publication guideline citation	Nutrient-specific recommendations	Specific recommendations for management of sarcopenia when on GLP-1 RA	Recommendations for nutrient support to manage digestive discomfort
Garber AJ et al. *Endocr Pract.* 2020;26(1):107-139.	N/A	N/A	N/A
Davies MJ et al. *Diabetes Care.* 2018;41(12):2669-2701.	N/A	N/A	"The dose of all GLP-1 RAs should be titrated gradually to minimize gastrointestinal side effects. These side effects can also be managed by reducing the carbohydrate content of the diet."
Raz I et al. *Diabetes Obes Metab.* 2018;20(6):1289-1299.	"Adequate intake of micronutrients such as magnesium, vitamin D and vitamin K may have beneficial effects on glucose metabolism and cardiovascular risk."	"Protein intake should be sufficient to maintain muscle mass and function."	"Gastrointestinal tolerability may be improved by adjusting meal composition, reducing fat intake, and increasing fiber intake."
American Diabetes Association. *Diabetes Care.* 2020;43(Suppl 1):S98-S110.	N/A	N/A	"Patients should start at low doses of GLP-1 receptor agonists and gradually titrate up to reduce adverse gastrointestinal effects."