What is the role of nutrition intervention in the age of highly effective anti-obesity medications?

Harold Bays, MD, FOMA, FTOS, FACC, FACE, FNLA, FASPC
Medical Director / President
Louisville Metabolic and Atherosclerosis Research Center
Clinical Associate Professor
University of Louisville School of Medicine

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Chair
Harold Bays

MD, FOMA, FTOS, FACC,
FACE, FNLA, FASPC

Speaker Bio

- Dr. Harold Bays is Board Certified in Endocrinology and Internal Medicine, Diplomate of the American Board of Obesity Medicine, and Diplomate of the American Board of Clinical Lipidology.
- He has served as an Investigator for over 600 Phase I - IV clinical trials regarding treatments for obesity, dyslipidemias, diabetes mellitus, hypertension, and other metabolic and hormonal disorders.
- Dr. Bays is Chief Science Officer of the Obesity Medicine Association and is Editor in Chief for Obesity Pillars – the journal of the Obesity Medicine Association.

Educational Goals

- Describe the nutrient intake of patients treated with GLP-1 RA based therapies
- Address the unmet nutrient needs of patients treated with GLP-1 RA based therapies
- Discuss optimal nutritional management and priorities for patients treated with GLP-1 RA based therapies
- Discuss lifestyle and behavioral interventions that enhance nutrition and health outcomes

What Happens to Dietary Nutritional Intake in Patients on GLP-1RAs?

What Happens to Dietary Nutritional Intake in Patients on GLP-1RAs?

- Most consistent effect of GLP-1RA is a reduction in caloric consumption (decreases by ~ 16 – 39%)
- Studies suggest GLP-RA have variable effects on the proportion of macronutrient consumption (fats, carbohydrates, proteins)
- Reduction in macronutrient intake may exacerbate underlying sarcopenia, or at minimum, accelerate lean body loss during weight reduction
- Reduction in micronutrient intake with GLP-RA may exacerbate underlying deficiencies (e.g., Vitamin D)
- Patients treated with GLP-RA may experience relative dehydration

Christensen S, et al. Obesity Pillars 2024;11:100121

What Are Nutritional Challenges in Patients on GLP-1 RAs?

What is Lean Body Mass?

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Lean body mass: Total body mass less stored fat in adipose tissue (i.e., lean body mass = water, mineral, protein, glycogen, and essential organ fat)

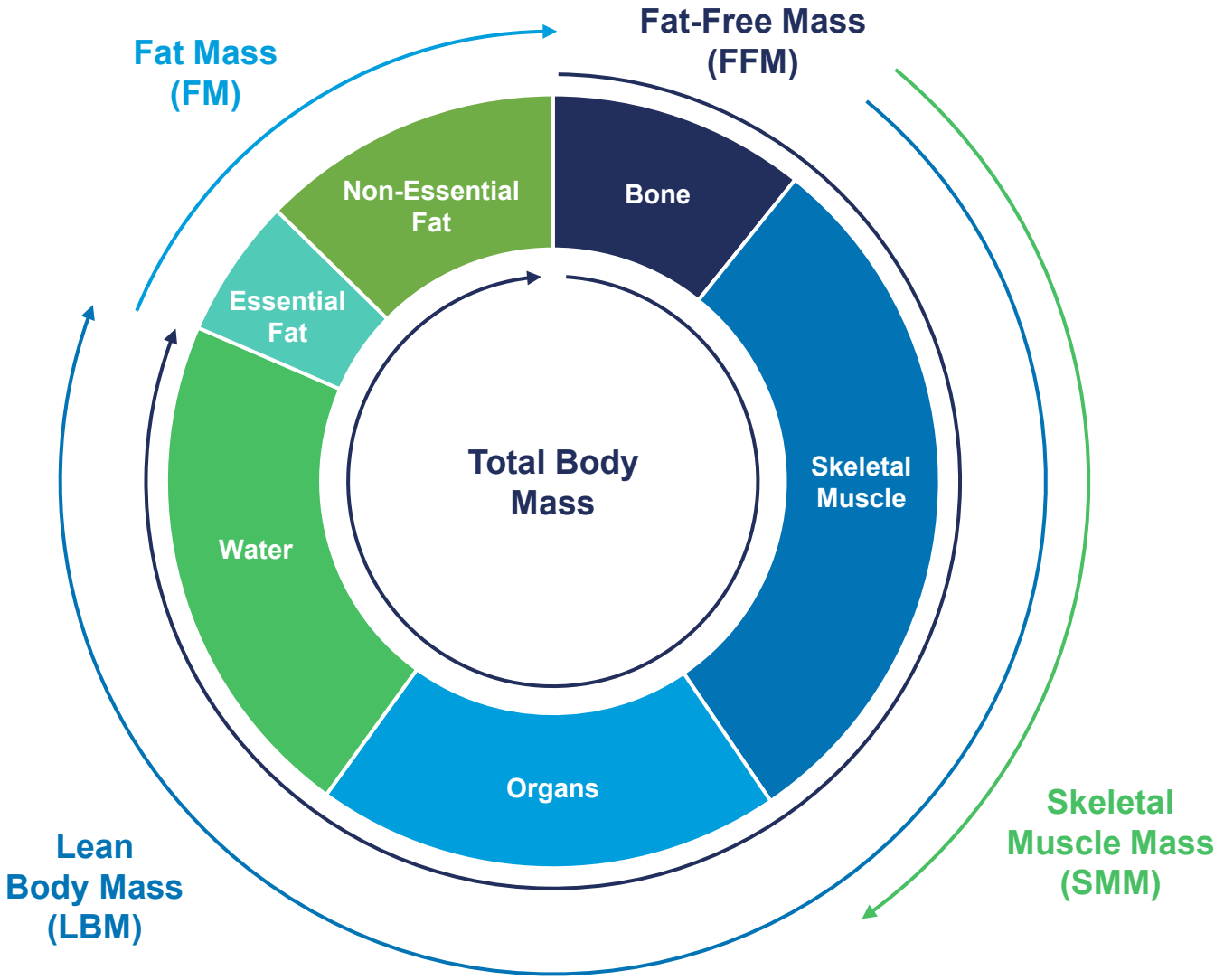
DXA definition of lean body mass: Lean mass = total mass – fat mass – BMC

In lean individuals, approximately 60% of body weight is water (i.e., water is 75% of the weight of muscle and body organs). In those with obesity, water weight can be as low as 40% of body weight due to the increased proportion of body fat that has relatively less water

Compared to Whites, percent body fat is generally lower among Blacks, and percent body fat is generally higher among Hispanic females compared to non-Hispanic Caucasian females. For lean individuals, lean body mass (LBM) is often 75% of total body mass (40% muscle, 10% bone, and 25% organs), and highly trained athletes may have LBM >85%

If not accompanied by healthful nutrition (e.g., protein) and ongoing resistance training, much of the reduction in lean body mass is due to a reduction in skeletal muscle

Burridge K, et al. Obesity Pillars, 2022;1:100007.
McCarthy D, et al. Nutrients 2021;13(7):2473.
Gallagher D, et al. Am J Clin Nutr 2017;105:78–84.



The components of fat-free mass, lean body mass, and skeletal muscle mass according to the definitions used by magnetic resonance imaging (MRI), dual energy X-ray absorptiometry (DXA), or computed tomography (CT) scans.

Nuijten MAH, et al. Obes Rev. 2022 Jan;23(1):e13370.

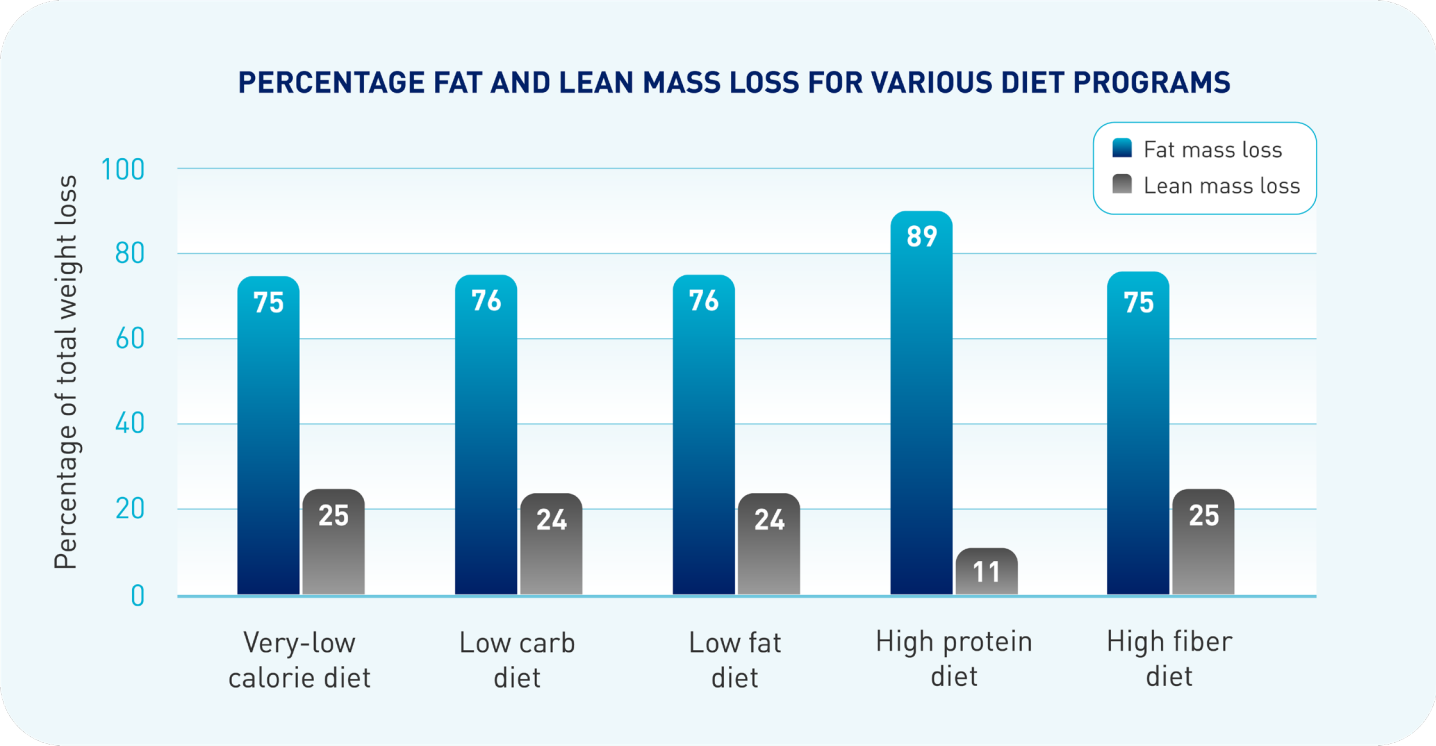
What is Sarcopenia?

Sarcopenic obesity: Reduction in muscle mass

- Multiple definitions with three themes: low muscle mass, strength, and physical performance
- Sarco-osteopenic obesity is the reduction in both muscle mass and bone mass
- Mitigation:
  - Healthful nutrition
  - Resistance training
  - Muscle sparing anti-obesity therapies

Smith C, et al. Ageing Research Reviews 2022;78:101617.

How Do Weight Reduction Interventions Affect Lean Body Mass?



Bariatric surgery may result in ~20 – 30% lean body mass loss, depending on the time after surgery (3 versus 12 months), with greater total weight reduction often found with bariatric surgery versus other interventions

Willoughby D, et al. Nutrients 2018;10(12):1876.
Nuijten MAH, et al. Obes Rev. 2022;23(1):e13370.

Illustrative Anti-Obesity Drugs in Development

FEATURED	OTHERS
GLP-1 RA: injectable and oral formulations	GIP RA
GLP-1 / GIP dual RA (i.e., like tirzepatide)	GCG analogue
GLP-1 / GCG dual RA	Ghrelin (“hunger hormone”) inhibitors
GLP-1 RA / GIP antagonists	Neuropeptide Y receptor antagonists (+GLP-1 RA)
GLP-1 / GIP / GCG tri-agonists	Leptin sensitizers
GLP-1 RA (semaglutide) / amylin analog (cagrilintide) (CagriSema)	Mitochondrial uncouplers
Muscle-acting agents	Oxytocin agonists (ERX1000)
Other gastrointestinal-acting agents	Sodium-glucose co-transporter- 1 & 2 inhibitors
Hunger suppressants and oral nutrient receptor agonists	G Protein-Coupled Receptor (GPR75)
	Dapiglutide (GLP-1/GLP-2 dual agonist)
	Cannabinoid receptor inhibitors

GLP: Glucagon like peptide-1; RA: Receptor agonists; GIP: Glucose-dependent insulinotropic polypeptide: GCG: Glucagon

Müller TD, et al. Drug Discovery 2022;21: 201-223
Chakhtoura M, et al. Lancet eClinicalMedicine 2023
Abdel-Malek M, et al. Internal and Emergency Medicine (2023) 18:1019–1030
Bays HE, et al. Obesity Pillars 2022;2:100018

Muscle Mass During Weight Reduction

During weight reduction: the proportion of weight reduction due to lean body mass reduction typically ranges between 25 – 50%

- Routine physical exercise (i.e., resistance training) and adequate protein intake may mitigate lean body mass reduction
- Absence of physical exercise and inadequate protein intake during weight reduction can exacerbate reduction in lean body mass

In **STEP 1 trial** of semaglutide, total placebo-corrected weight reduction was 12.7 kg.

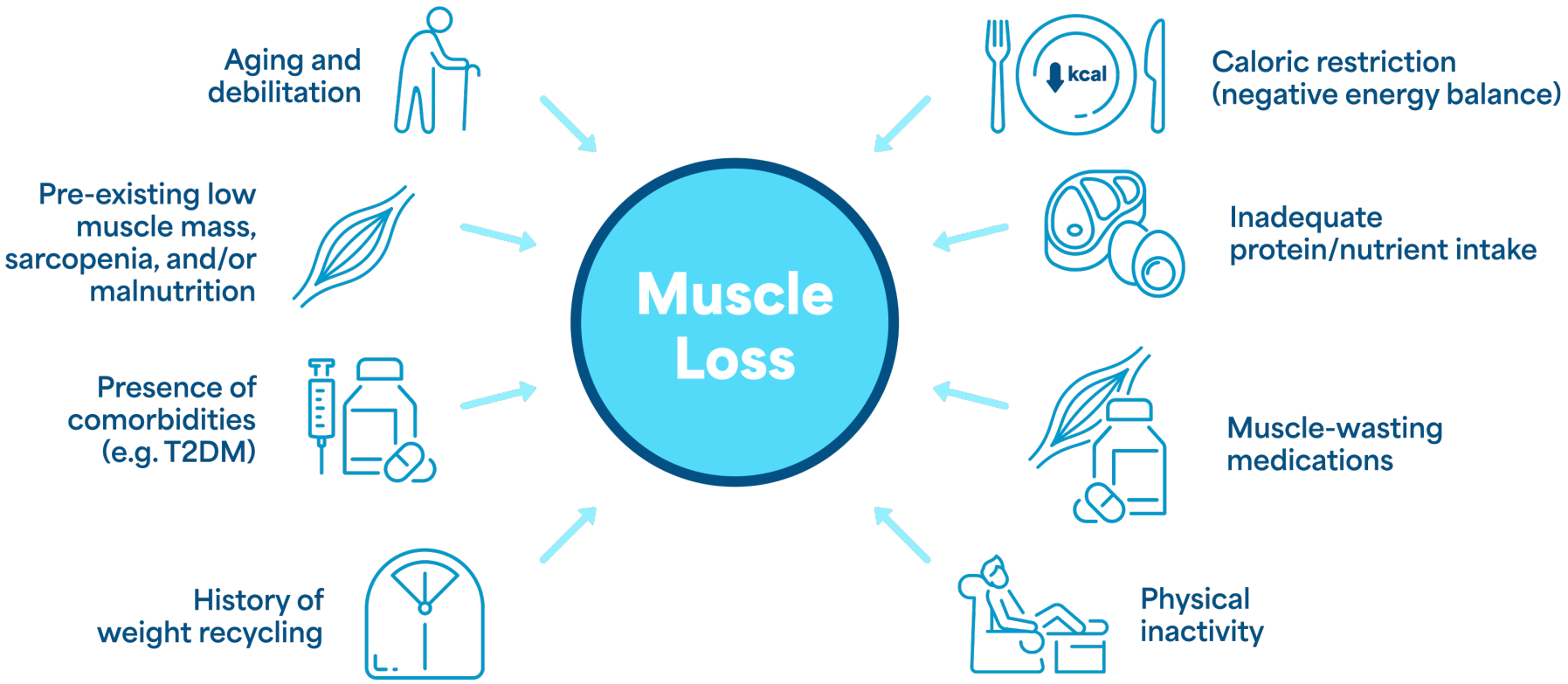
In DXA sub-study compared to placebo:

- Total fat mass reduction of 9 kg (20 lbs) and lean body mass reduction of 5.4 kg (12 lbs)
- Total weight reduction 9 kg + 5.4 kg = 14.4 kg. 9/14.4= ~60% of total weight reduction due to changes in fat
- ~40% weight reduction due to changes in lean body mass (i.e., muscle)
- Has implications regarding older patients and patients with sarcopenia and osteopenia

Neeland IJ, et al. Diabetes Obes Metab. 2024;26:16–27

Wilding JPH, et al. J Endocrine Soc. 2021;5 (Supplement_1):A16-A17

Factors Associated with Muscle Loss during GLP-1 based Therapy

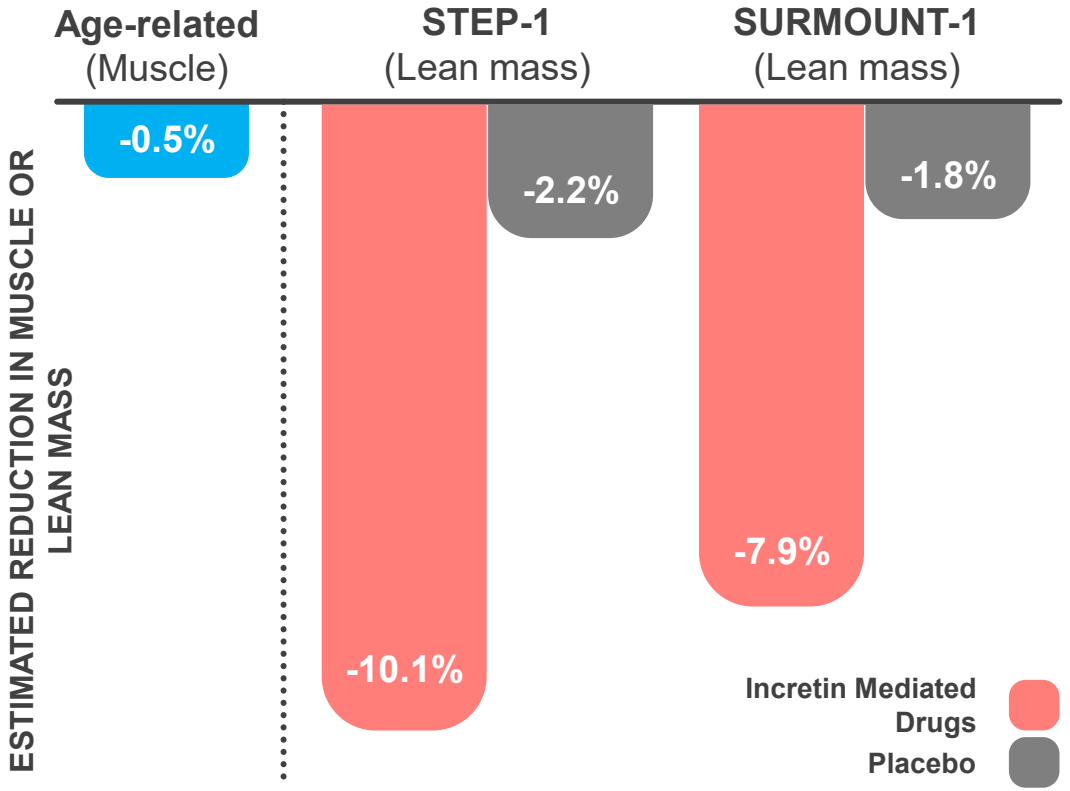


Adapted from Mechanick JI, et al. Obesity Reviews 2024;e13841

Estimated Loss of Muscle or Lean Mass in a Year

*"The estimated loss of skeletal muscle in STEP-1 and SURMOUNT-1 trials (≥10% during 68– 72 weeks of treatment) approximates the average decline in muscle mass during 20 years of aging-related muscle loss in adults."**

* Yearly age-related muscle loss in adults older than 30 years is estimated at 3%–5% per decade



Estimated yearly age-related muscle loss in adults and estimated declines in total lean mass during the first year of IMD therapy in the STEP-1 and SURMOUNT-1 trials. Estimated declines in total lean mass during the 68-week STEP-1 and 72-week SURMOUNT-1 trials were normalized to 52 weeks based on the simplifying assumption that the decline in lean mass was linear over time.

Adapted from Mechanick JI, et al. Obesity Reviews 2024;e13841

Muscle-Acting Agents (Mass, Function, and Approval)

Activin receptor antagonists

- Activin receptors regulate growth, cell differentiation, homeostasis, osteogenesis, apoptosis; activin is a negative regulator of muscle mass
- Bimagrumab is a human monoclonal antibody that binds and inhibits activin receptor type-2B

Myostatin (growth differentiation factor 8 or GRD8) inhibitors

- Myostatin is a negative regulator of myoblast proliferation and differentiation (i.e., induces muscle wasting contributing to cachexia)
- Trevogrubab is a monoclonal antibody that targets myostatin; Garetosmab is a monoclonal antibody that targets activin
- Trevogrumab, with or without garetosmab, is being evaluated in patients with obesity treated with semaglutide

Apelin agonists

- Apelin increases skeletal muscle mitochondrial function and biogenesis
- Azelaprag (BGE-105) apelin receptor agonist being co-administered with tirzepatide

Anabolic agents

- Enobosarm (ostarine) is a non-steroidal androgen receptor modulator being evaluated to mitigate muscle loss with anti-obesity medications

Muscle energy expenditure maintaining agents

- Growth differentiating factor 15 (GDF15) reduces obesity and improves glycemic control through glial-cell-derived neurotrophic factor family receptor α-like (GFRAL)-dependent suppression of food intake
- May counteract compensatory reductions in energy expenditure and maintain energy expenditure in skeletal muscle during caloric restriction and weight reduction

Müller TD, et al. Drug Discovery 2022;21: 201-223
Chakhtoura M, et al. Lancet eClinicalMedicine 2023
Abdel-Malek M, et al. Internal and Emergency Medicine 2023;18:1019–1030
Bays HE et al. Obesity Pillars 2022;2:100018

Measures of muscle anatomy

- DXA
- MRI

Measures of muscle function

- Step devices
- Motion devices
- Stair devices
- Walk test

Successful Nutrition Care Alongside GLP-1 RAs: Key Factors for Long Term Sustainability

1. Multi-disciplinary approach beyond medication adjustment
   - Dietary guidance, behavior & lifestyle modification, regular patient monitoring
2. Education
   - Structured educational approaches, e.g. visual aids and metaphors
3. Patient-centered
   - Personalized diet plans, monitor GI AEs and risk of undernutrition
4. Hydration
   - Maintaining renal function and preventing dehydration

Despain D, et al. Obesity Pillars 2024;12:100143

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