

Health, risks and disease in therapeutic functionalities of Glucagon-like peptide-1 receptor agonists (GLP-1RAs) concerning human susceptibility

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Abstract: This review expounds the unique sphere of medical care as it ardently advances the therapeutic concerns and essentials of GLP-1 drugs per the risk of inappropriate lean mass loss, possible resultant sarcopenia, with special reference in elderly or frail persons, irrespective of the beneficial outcomes of weight loss in chronic perturbations, such as type 2 diabetes, obesity, comorbidities, cardiovascular and neurodegenerative disorders. It is significant to have protective stances on muscle quality. The proportional augmentation of muscle lost with GLP-1 usage requires inter alia resistance training, high protein consumption, and potential medication research to ameliorate muscle wasting. These highlight the pertinence for an equilibrated modality to obesity, type 2 diabetes and cardiovascular disease management, incorporating lifestyle changes for the sustainability and preservation regarding the functional status and stance as well as the quality of life. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are comprehensively utilized for the improvement of glycemic regulation and inducement of weight loss in type 2 diabetes (T2D), however, therapeutic outcomes vary tremendously among patients. GLP-1 receptor agonists (GLP-1 RAs) are being advanced from diabetes and obesity therapeutic regimen to novel spheres for disparate emerging conditions, encompassing cardiovascular, hepatic, neurodegenerative, and autoimmune perturbations, and may provide benefits in attenuating muscle dissipation by lean muscle mass preservation, although human data are anecdotal necessitating ardent studies. GLP-1 drugs are not directly the causative agents in muscle shrinkage, however, the prominent weight loss these drugs potentiate may preponderate to the dissipation of lean body mass, including muscle. The muscle loss may exacerbate in persons with pre-existing sarcopenia or other untoward health states. Although, certain muscle loss is inherent to an extent of accelerated weight loss, it is conducive to realise that the access to resistance training and proper protein intake in patients, vulnerable or susceptible individuals may ameliorate this impact and cause weight loss to be safer and increasingly sustainable. Invariably, GLP-1 drugs are aetiologic agents in muscle shrinkage, concomitantly with accelerated weight dissipation as the body utilises both fat and muscle for energy, with certain research indicating lean body mass, in concert with muscle, responsible for appreciable amount of overall weight loss. In order for these to be averted, coupling of GLP-1 with a high-protein diet and resilient physical training or exercise for muscle mass preservation may be pertinent. The broad and progressive advantages of GLP-1 medicines, primordially emanated as therapeutic target developed for regulating blood glucose and weight which improved outcomes and good prognosis in persons presenting with heart, kidney, liver, arthritis, and sleep apnea dysfunctions. The actions mediated partly via anti-inflammatory and metabolic pathways, and certain benefits partly independent of the extent of weight loss. The role or function of GLP-1 receptor agonists encompass lowering of serum glucose concentration with concomitant management of metabolism in patients implicated. The emerging functionality of Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) primordially developed for type 2 diabetes management, have evolved into prominence in obesity management, providing clinically purposeful and beneficial weight loss and numerous other clinical trials in health and disease for the future.

Keywords: obesity, type 2 diabetes, neurdegenerative disorders, cardiovascular anomalies, muscle dissipation, weight loss, sarcopenia.

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INTRODUCTION

The glucagon-like peptide-1 (GLP-1) receptor or GLP-1R, is a primal ingredient of the G protein-coupled receptor (GPCR) category that is essentially located on the exterior of diverse cells inside humans. This receptor concisely interacts with GLP-1, a pivotal hormone that functions integrally in the regulation of blood glucose concentrations, lipid metabolism, and numerous vital biological mechanisms. Recently, GLP-1 therapies have assumed the fulcrum in the medical sphere as a result of their newfangled therapeutic processes, important treatment efficacies, and expansive progressive possibilities. The essential objective of most related research is the emphasis on the broad advantages of the application of GLP-1RAs in therapeutic measures in an extensive array of disorders, such as non-alcoholic fatty liver disease (NAFLD), oncological issues, cachexia, musculoskeletal inflammation, obesity, diabetes including cardiovascular and neurodegenerative disorders. The contemporaneous enactment and development of nascent advances in GLP-1 drugs provide promising opportunities for expansion in therapeutic interventions, depicting vital events in the medical arena [1].

Glucagon-like peptide- 1 receptor agonists (GLP-1 RAs) are categorized as treatment regimens which are recommended for chronic disorders [2]. Nowadays, there are extant paucity and anecdotal evidence on the impact of GLP-1 RA regarding body composition among elderly individuals as well as patients presenting with chronic nephrotic, hepatic and inflammatory bowel disorders. Although, GLP-1 RA can lead to total weight loss in excess of 25%, contemporaneous investigations indicate that there could be superimposed remarkable dissipation of lean body mass extending to as much as 15-40% depreciation of total weight. The rapid and marked decline in muscle mass due to the consumption of GLP-1 RA exposes a cross-section of the exposed and vulnerable patient populations presenting with sarcopenia to an elevated risk to muscle dissipation and excruciating presentations. Thus, in essence, this review explores varied factors which may be the prime aetiology for accelerated muscle loss among highly susceptible risk and vulnerable patient populations, with marked interventions to mitigate the risk of unabated sarcopenia and inter alia the characteristic frailty [3].

Indications of muscle wasting disorders constitute the most deleterious and grave noncommunicable or chronic disease conditions. Muscle wasting coexists with disparate neuromuscular disorders, myopathies, cancer, cardiac failure, chronic respiratory impairments, kidney disorders, peripheral neuropathies, inflammatory diseases and musculoskeletal debilities. Contemporaneous therapy approaches are somewhat ineffective and provide restricted rate of muscle degeneration. These include nutrient supplements, appetite stimulants and immunosuppressants

potentiated to exacerbate muscle dissipation. The most therapeutic strategy in to impair myostatin and activin receptor signaling due to these circulating factors are potent inhibitors of muscle development, growth and regulators of cell differentiation for muscle progenitors. Studies have exhibited the clinical prowess of counter suppressing the inhibitors, augmenting the protein synthesis of muscle cells, ameliorating decadence, promoting mitochondrial biogenesis, and muscle function preservation. These sorts of modifications are capable of impeding muscle wasting in disparate disease animal models but numerous drugs which target this pathway are unsuccessful during clinical trials, severe therapy-associated deranging incident or off-target events. No successful interactions may result from incapability to enhance muscle functionality irrespective of the preservation of muscle mass. Potential drugs encompass antibodies and gene therapeutics, with differential targets thus, safety, efficacy, and defined profiles, designed uniquely with intendment in revolutionising treatment of both acute and chronic muscle dissipation, or combinatorially with other developing or novel therapeutics for related muscle pathologies or metabolic disorders [4].

Accelerated weight loss with GLP-1 receptor agonists may result at the expense of skeletal muscle in concert with deterioration of metabolic and functional events. This review highlights the emergence and reemergence of palpable evidence which give precedence for clinical and epidemiological approaches to muscle preservation in ensuring long-run prognosis of drug therapeutic muscle mass regimens [5]. It is suggested that a diet enriched in protein and coupled with resilience and resistance training may be beneficial in the prevention of muscle mass dissipation from the consumption of GLP-1 RAs. A target and delivery of personalised nutrition and physical activity regimen instituted for a specific patient focussed on the optimisation of protein intake and frequent resistance training can mitigate muscle mass loss concomitantly with enhancement of fat mass dissipation. Future Studies are pertinent to evaluate and monitor the impact of GLP-1 RA on sarcopenia within high-risk ambients [2, 3]. Also, this article reviews glucagon-like peptide-1 receptor agonists (GLP-1RAs) and their emerging therapeutic applications, with an emphasis on potential untoward impacts encompassing muscle loss and sarcopenia risk, with particular reference to the elderly populations. It outlines modalities for diminishing muscle mass loss including resistance training and protein intake as well as highlighting the benefits of GLP-1RAs in obesity, diabetes, and several chronic diseases. Implicit assumptions indicate that these therapies are expansively contextually applicable to chronic impairments and muscle mass dissipation.

Challenges, issues and opportunities of GLP-1 drugs in therapies



GLP-1 receptor agonists (GLP-1RAs) provide systemic health benefits, such as weight depreciation, blood pressure improvement, and lowered cardiovascular risk, however, bearing risks, for instance, nausea, vomiting, diarrhea and potential for acute kidney perturbations, frequently associated with gastrointestinal effects, while other risks are injection site reactions and, for select medications, a black box alarm concerning a prior of medullary thyroid cancer, while certain data present potential muscle mass dissipation [2, 3, 5]. The impacts of GLP-1 agonists on muscle undergo inordinate amount of polemics, with certain data or evidence depicting muscle shrinkage and sarcopenia risk, whereas other studies arrogate positive effects on muscle quality and functionality on diminished inflammation and metabolic health improvement. Pivotal issues are the percentage of lean body mass loss, the repercussions for functional deterioration in vulnerable persons, and dearth of specific muscle data other than total lean mass. Strategies to mitigate untoward effects include resistance training, adequate protein intake, and potentially investigational therapies to preserve muscle [2, 6, 7]. GLP-1 agonists can cause clinically significant lean body mass (LBM) loss during weight reduction, posing a risk for muscle shrinkage, especially in vulnerable populations like older adults or those with pre-existing chronic conditions, potentially contributing to sarcopenia and frailty. However, evidence is mixed, with some studies suggesting beneficial effects on muscle, including reduced fatty infiltration. Therapeutic strategies to mitigate this risk include resistance training, adequate protein intake, and potentially co-administered agents like myostatin inhibitors [2, 8]. GLP-1 drugs can precipitate muscle mass loss concomitantly with rapid weight loss, but experts dissuade against untoward concern about the side effect when applied with lifestyle patterns or modifications correlated to resistance training and a high-protein diet ingestion. There is progressive development of strategies to prevent muscle loss in the application of GLP-1 therapy, using dual blockade of the proteins activin A and myostatin, which can suppress muscle growth and development. GLP-1 medications have altered obesity [9] and diabetes [10] treatment, but are capable of also inducing the risk of muscle loss. Inasmuch as it is advisable for patients to ingest an enhanced protein diet for muscle mass preservation, it is uncertain to decipher the desired quantity or quality of the diet or training in the absence of a physiotherapist or nutritionist. In this regard, the provision of real-time feedback becomes increasingly pertinent, particularly for patients on GLP-1 regimen, the elderly, or those presenting with sarcopenia [11-13]. The vital functionalities of skeletal muscle are currently within public purview due to data availability on the application of GLP-1 receptor agonists which effect weight loss, but can trigger pronounced evidence of muscle dissipation. It is suggested that muscle loss associated with these therapeutic regimens (as determined by decrement in fat-free mass [FFM])

extends from 25% to 39% of the overall mass lost in excess of 36–72 weeks [14]. The significant muscle loss is attributable to the extent of weight loss, in contrast to an independent impact of GLP-1 receptor agonists, as may be elucidated in future studies. Conversely, non-pharmacological caloric restriction research with decreased scope of mass loss culminates in 10–30% FFM dissipation [15]. In context, on an annual basis, the decline in muscle mass with GLP-1 receptor agonists is several times greater than what would be expected from age-related muscle loss (0.8% per year based on 8% muscle loss per decade from ages 40–70 years). Neglecting the relevance of muscle dissipation creates a disconnect between the increased awareness of muscle by patients and its role in health, and clinicians who relegate these concerns to the background, influencing adherence to and development of optimum therapy modalities [11]. GLP-1 receptor agonist therapies induce substantial weight loss, but up to 40% of this weight loss is lean mass, particularly muscle. Loss of muscle mass can be precipitated via activation of type II activin receptors ActRIIA and/or ActRIIB, and blockade of these receptors can result in muscle growth and development. An approach is extant for preventing muscle mass loss in GLP-1 receptor agonist therapy by combined blockade of the ActRIIA and ActRIIB ligands GDF8 (myostatin) and activin A. Diet-induced obese mice were treated with either a vehicle control, a sole GLP-1RAs receptor agonist semaglutide, or GDF8 and activin A antibody blockade alone (α MSTN- α ActA) or semaglutide and α MSTN- α ActA. The combination therapy of semaglutide and dual GDF8 and activin A blockade culminated in similar content in total body weight loss to merely semaglutide, but with statistically significant elevated shielding from lean mass dissipation and pronounced decrement in proportion of fat mass to only semaglutide [12].

Weight loss due to glucagon-like peptide-1 receptor agonists (GLP-1RAs) and combined dual glucagon-like peptide-1 receptor (GLP-1R)/glucose-dependent insulinotropic polypeptide (GLP) receptor agonists is approaching the extent enacted within the surgery domain. In the event of excess mass loss, concern pertains for potential side effects on the substance, morphology and health of skeletal muscle mass. The heterogeneity exhibited in the effects of GLP-1-based therapies on lean mass alterations in certain clinical trials and studies include decrements in lean mass range of 40% to 60% of total mass loss but disparate investigations depict lean mass decrements circa below 16% of total mass loss. Severally, there are extant reasons for heterogeneity, such as population-based, drug-specific/molecular, and comorbidity impacts. Superimposed on these, are modifications in lean muscle mass may not invariably depict alterations in muscle mass as the erstwhile measure inculcates not merely muscle but other organs, fluid, and water in fat tissue. Contemporaneous addition of magnetic resonance imaging-based investigations, skeletal



muscle alterations using GLP-1RAs treatments are ostensibly adaptive: decreased muscle volume appears to be commensurate with predicted achieved ageing, disease status, and weight loss. The improved insulin sensitivity and muscle fat infiltration ostensibly contribute to an adaptive mechanism with enhanced muscle quality, retarding the probability for loss in power and morphology. Factors such as advanced age and disease severity may impact conducive and proper selection of candidates for these therapies due to sarcopenia risk. For improvement of muscle health in the event of muscle mass loss, a number of pharmacologic therapeutic modalities for the sustenance or improvement of muscle mass targeted and delivered in combined form with GLP-1-based therapies are pertinent, with focus on precision, accuracy and purposeful assessments of muscle mass composition, functionality, mobility and strength for sustainable impact on muscle health for the inordinate number of patients who may be connected with these medications into the future [16]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have modified obesity management, thus depicting proficient efficacious weight loss and progressive improvement metabolic spheres. Evidence suggests that these agents are unintended consequences for the reduction in skeletal muscle mass, potentiating, exacerbating or precipitating sarcopenic obesity, especially in frail and elderly persons presenting with restricted muscle mass reserves. Despite the central role of GLP-1 RAs therapy to the management of obesity, early optimization of its application and management of its correlated risks and sequelae is essential for the sustenance of skeletal muscle health, well-being, functional status and quality of life of a patient.

On the whole, the role of GLP-1 RAs has extended beyond mere glycaemic control in type 2 diabetes to emerge as the hallmark in obesity management. It is increasingly suggested that the prominent weight loss associated with GLP-1 RAs is accompanied by decreased skeletal muscle mass and the risk of sarcopenic obesity, particularly in elderly individuals. Integrating exercise, adequate protein intake, and potentially adjunctive pharmacotherapies is essential to mitigate this risk. With increase in the clinical application of GLP-1 RAs, it becomes paramount to optimally understand their long-run impact for their optimized utility and sustenance of skeletal muscle health, morphological stance, and quality of life of patients [17] as well as susceptible and vulnerable individuals.

Exploring continuous protein sensor for sarcopenia management

The onset of sarcopenia is inextricably linked with ageing, presenting profound consequences not for the quality of life of merely a patient but for that of a more expansive global healthcare scheme. Prompt and precise determination of sarcopenia and a holistic

comprehension of its mechanism and therapeutic targets are primordial for effective handling of the condition [18]. Thus, newfangled GLP-1 therapies improve weight loss through the sustenance of muscle mass that is pivotal in comprehensive health and wellbeing in obesity treatment. Research presented at the 2025 American Diabetes Association (ADA) Scientific Sessions highlighted a combination therapy of semaglutide, a GLP-1 agonist, and bimagrumab, a drug targeting muscle dissipation. Furthermore, a nascent continuous biosensor for muscle breakdown, and modalities, such as regular exercise or training and normal protein intake are beneficial for the augmentation of muscle health in patients on GLP-1 pharmacotherapies [19].

In order to manage sarcopenia, a continuous protein sensor tracks the protein status of the body in real-time, thereby providing vital feedback, particularly to elderly persons and individuals using medications, such as GLP-1 receptor agonists, to achieve proper protein intake for muscle sustenance. Current studies have unravelled that wearable phenylalanine sensors monitor protein consumption, and offers increasingly personalized and effective sarcopenia management by means of targeted delivery of nutritional interventions and physical training or exercise. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are predominantly effective in both weight loss and glycemic control in obesity and/or diabetes but with resultant sarcopenia exhibiting loss of lean muscle mass (LLMM) [20]. The impact of LLMM can be suppressed by augmenting protein intake and physical training or exercise [21]. As an essential amino acid that is discharged during the breakdown of skeletal muscle, phenylalanine (phe) and available for exogenous protein ingestion, a wearable phenylalanine sensor having an activity monitor is competent to track LLMM and protein intake applying these transformative therapies. This sensor applies a novel approach that is dependent on a facilitated phenylalanine bioreceptor in concert with a short nucleic acid sequence (aptamer) with labeled methylene blue redox probe, attached to an electrode surface for binding. The phenylalanine level is determined by means of the electrochemical square wave voltammetry method. This exhibits a proof-of-concept continuous protein monitor engineered bioreceptor on a microsensor array that is utilisable with GLP-1 RA therapy [22].

Sarcopenia is characterised by incessant risk of falls, morbidity, and mortality. Proper diet and exercise constitute the main strategies to define sarcopenia. Sustained high-quality diet is a perennial modality for muscle health preservation. Protein and the amino acid, leucine undergirds muscle trophism and the sustainability of lean mass into old age. Recent technologies may help to define nutritional strategies for to meet the necessities of elderly individuals [23]. As sarcopenia is a geriatric state featuring progressive



dissipation of skeletal muscle mass and strength, concomitantly with elevated risk for adverse health prognosis, such as falls, frailty, institutionalization, diminished quality of life, morbidity and mortality. Currently, defined pharmacologic therapeutic regimens are unavailable to diminish sarcopenia development, stemming its progression, or inhibiting its untoward health prognosis. The most effective approaches to contrast sarcopenia is dependent on healthier lifestyle, adherence to high-quality diets and regular exercise. Research must focus on special dietary protocols to stem age-associated muscle wasting, in conjunction with the putative mechanisms. Focus on the challenges, issues and opportunities associated with the design and implementation of effective nutritional patterns and the proper timing of nutritional interventions to sustain muscle health and morphology must be emphasized into advanced ageing [24].

Weight dissipation due to dietary calorie restriction, bariatric surgery or pharmacologic therapies emanate from fat mass loss related to pronounced excoriation in fat-free mass (FFM), identical to skeletal muscle mass (SMM). The repercussions of glucagon-like-peptide-1(GLP-1)-based medications on muscle mass and function, polemically suggest a higher risk of sarcopenia whereas others suggest certain protection against sarcopenia. A vast majority in vitro and in vivo animal experimentations depict beneficial effects of GLP-1-based therapies on muscle mass and function, significantly by diminishing inflammation and benefitting mitochondrial health. A majority of findings are rather reassuring in humans, paving the trajectory for clinical studies using validated approaches to better comprehend the impacts of GLP-1-based medications on muscle mass, power, morphology and the potential risk of sarcopenia in at-risk or susceptible elderly frail individuals [7].

Glucagon-like peptide-1 (GLP-1)-based therapies impose a clinically pertinent skeletal muscle mass loss, associated with total better outcome in type 2 diabetes and/or clinical obesity. A risk of excess excoriation in fat-free mass (FFM) and skeletal muscle mass (SSM), potentiates sarcopenia in at-risk patients, thus, constituting a controversial sphere of untoward events which diminishes the benefit/risk balance. The maximizing of fat loss while preserving lean (muscle) tissue mass and function constitutes the pivotal objective of prevailing obesity pharmacologic therapies. Available data do not present definite conclusive findings of positive/negative effects of GLP-1-based therapies on muscle. Future excursions enabling trustworthy strategies to evaluate not merely SMM but muscle morphology, power and mechanistic disposition are pertinent for the optimum analysis regarding the impact of GLP-1-based therapies, particularly within persons vulnerable to sarcopenia, elderly and frail individuals. [7].

Glucagon-like peptide-1 receptor agonists, obesity, diabetes and muscle dissipation

Glucagon-like peptide-1 receptor agonists function by means of appetite inhibition and caloric restriction. The therapeutic regimen is capable of culminating in pronounced muscle loss, ostensibly due to evolutionary mechanisms shielding against food scarcity since muscle represents a putative energy predator. A process that diminishes muscle mass is the activation of type II activin receptors, ActRIIA/B, which produce proficient muscle development and growth in humans in blockage. There was demonstration of GDF8 (myostatin) and activin A being the two principal ActRIIA/B ligands mediating muscle minimization. It was reported that dual blockade prevented muscle loss linked with glucagon-like peptide-1 receptor agonists, and augmented muscle mass in both obese mice and primates other than humans. The muscle preservation accelerates fat loss and exhibits metabolic benefits. Ostensibly, repositioning glucagon-like peptide-1 receptor agonist therapy with GDF8 and activin A blockade can immensely improve the quality of weight loss during human obesity treatment [25].

The global increase in obesity and type 2 diabetes mellitus (T2DM) depicts significant challenges, issues and opportunities in musculoskeletal care, augmenting increased perioperative sequelae, deranged bone health, and suppressed muscle functionality. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), incipiently produced for glycemic control in T2DM, have exhibited prominent benefits in weight decrement and metabolic regulation. It is purposeful to recognize and elucidate the musculoskeletal biologic and clinical impacts of GLP-1RAs [26]. Evidence suggests that GLP-1RAs affect musculoskeletal health via anti-inflammatory effects, bone metabolism modulation, and modifications in muscle composition. GLP-1RAs may cause osteoblastogenesis while diminishing osteoclast functionality for the sustenance of bone mineral density. Furthermore, while GLP-1RAs induce lean mass loss, GLP-1RAs apparently preserve skeletal muscle, suppress fatty infiltration, and augment fibre production and functionality. Superimposed on these, GLP-1Rs are available in synovial tissue and cartilage, establishing downregulation of inflammatory molecules and chondrocyte apoptotic pathways, but clinical research exhibit variations in osteoarthritis setting. On the whole, the heterogeneity in results, paves the trajectory for further research to delineate the long-run musculoskeletal impacts of GLP-1RAs [26]. Elucidating the musculoskeletal impact of GLP-1RAs is vital in the optimization of their inclusion into orthopaedic practice. Exploration of the orthopaedic consequences of GLP-1RAs may unravel their biologic mechanisms and clinical impacts on obesity-associated joint inflammation and arthropathy as well as bone mineral density, fracture risk and preservation of skeletal muscle [26].



Glucagon-like peptide-1 receptor agonists and chronic disorders

At inception, GLP-1 receptor agonists (GLP-1RAs), approved for obesity and diabetes management are currently being scrutinized concerning neuroprotective sequelae in an array of neurological impairments. The receptors of these agents are expansively experienced in brain precincts correlated with cognition and metabolism, modulation and neurotransmitter discharge as well as neurogenesis enhancement. Contrary to findings that preclinical investigations consistently depict advantages in models of Alzheimer, Parkinson, multiple sclerosis, and amyotrophic lateral sclerosis (ALS), certain results indicate that outcomes of clinical trials have exhibited variations, broadly due to presenting heterogeneous study populations and trial design or framework. Nascent agents, such as NLY01 and tirzepatide, are being developed for enhanced central nervous system accessibility and efficacy. Inasmuch as GLP-1RAs are presumably innocuous in metabolic states, their applications in neurological disorders necessitate proper patient evaluation, monitoring and selection. Future trajectories involve the development of pertinent and precise biomarkers, implementation of defined medical modalities and exploration of using combined therapies for the optimum maximization of therapeutic potential [27] or potentiality

The glucagon-like peptide-1 (GLP-1) receptor or GLP-1R, is a primal ingredient of the G protein-coupled receptor (GPCR) category that is essentially located on the exterior of diverse cells inside humans. This receptor concisely interacts with GLP-1, a pivotal hormone that functions integrally in the regulation of blood glucose concentrations, lipid metabolism, and numerous vital biological mechanisms. Recently, GLP-1 therapies have assumed the fulcrum in the medical sphere as a result of their newfangled therapeutic processes, important treatment efficacies, and expansive progressive possibilities. The essential objective of most related research is the emphasis on the widespread advantages of the application of GLP-1RAs in therapeutic measures in an extensive array of disorders, such as non-alcoholic fatty liver disease (NAFLD), oncological issues, cachexia, musculoskeletal inflammation, obesity, diabetes including cardiovascular and neurodegenerative disorders. The contemporaneous enactment and development of nascent advances in GLP-1 drugs provide promising opportunities for expansion in therapeutic interventions, depicting vital events in the medical arena [1].

Glucagon-like peptide-1 receptor agonists are a class of drugs which mimic a natural incretin hormone released by the intestine after meals, and are compatible for type 2 diabetes treatment. Glucagon-like peptide-1 receptor agonists also contribute to satiety and diminished appetite or craving for food via action on the appetite regulation centres of the brain, with resultant weight

dissipation in obese patients. Since glucagon-like peptide-1 receptor agonists retard gastric discharge, a precautionary measure in patients under deep sedation or general anesthesia concerning gastric aspiration and the prolonged half-life in the blood are concerns of difficulty in the management within the perioperative stance. It is purposeful (i) to explore the current data regarding the risk of aspiration prior to anesthesia; (ii) to explicate the methodology in the evaluation of available liquid and food in the stomach antecedent to surgery; and (iii) to equilibrate the exact precautionary measure with the potential for future discovery taking benefits into cognizance [28].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have transformed obesity management, substantial weight loss and metabolic benefits. In addition to obesity and type 2 diabetes, the therapeutic potential of GLP-1 RAs preponderates to other debilitating untoward states, such as disorders of cardiovascular, hepatic, neurodegenerative, and substance abuse spheres. Although, early concerns of pancreatic and thyroid cancer have been extensively ameliorated according to current evidence, the presentations of gallbladder and biliary diseases, impaired mental functions, and perioperative aspiration risk necessitate constant investigations. Furthermore, indications of weight recompensation following therapy disruption and decrements in lean mass define the necessity for protracted, personalized approaches to preserve better clinical prognosis. The exorbitant pecuniary outcome and restricted access to these therapies invoke crucial policy and equity challenges, issues and opportunities. Future Ardent research must focus on these gaps [29], addressing the long-run safety, optimization of holistic strategies, evaluation [30] and monitoring of an expansive clinical and economic burden in GLP-1 RA application.

Metabolic dysfunction-associated steatotic liver disease (MASLD)

Metabolic dysfunction-associated steatotic liver disease (MASLD) pertains to the predominant fat aggregation in the hepatic organ due to substances excepting intake of drugs and alcohol or intoxicants. Globally, it is the most ubiquitous hepatic disorder with accelerating prevalence among persons presenting cardiometabolic comorbidities. Although, lifestyle changes remain the primordial strategy in the management of MASLD, the effectivity is frequently restricted, underscoring the pertinence for extra therapeutic choices. The USA Food and Drug Administration gave approval for resmetirom as the first drug of choice for MASLD in 2024 following its established histological efficacy in the management of both steatohepatitis and fibrosis in an expansive Phase III trial, with desired safety and tolerance profile. Currently, incretin-based therapies and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), disparately or in conjunction with glucose-dependent insulinotropic polypeptide and/or glucagon



receptor agonists, have exhibited fruitful outcomes in diminishing concentrations of liver enzymes with improvement of MASLD, especially in the reduction of hepatic steatosis [31].

Non-viral aetiologies have increasingly induced hepatocellular carcinoma (HCC), particularly metabolic impaired-associated steatotic liver disease (MASLD) that is ubiquitous in type 2 diabetes mellitus (T2D). There is no extant pharmacological agent that is given approval for HCC chemoprevention. Patients with MASLD and T2D, SGLT2 inhibitor usage were associated with lower risks of HCC and all-cause mortality in contrast to active comparables. When residual confounding variables or factors are not exclusive, these results undergird prospective evaluation of SGLT2 inhibitors for hepatic-risk amelioration in the population [32]. Regarding their multiorgan impacts, GLP-1 receptor agonists are progressive therapeutic strategies in MASLD treatment. Prevailing evidence indicate that GLP-1 RAs, particularly liraglutide and semaglutide, can improve liver fat concentration and biomarkers of liver functionality. [30]. GLP-1 receptor agonists (GLP-1 RAs) are distinctly evolving into a reliable treatment for metabolic dysfunction-associated steatotic liver disease (MASLD) by decreasing liver fat, inflammation, and fibrosis by mechanisms, such as weight loss, improved insulin sensitivity, and direct impacts on hepatic cells. As semaglutide has depicted pronounced efficacy, broader large-scale, long-run research could be conducted to establish the functionalities in fibrosis regression and confirm GLP-1 RAs as a formal MASLD therapy [30].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) generally improve glycemic control and induce weight loss in type 2 diabetes (T2D) with varied significant treatment responses. It is hypothesised that eating behaviour impact on therapeutic efficacy, but there is paucity of undergirding evidence. The study depicted that GLP-1RAs improve both metabolic parameters and external food intake behaviour in patients having T2D with external eating emerging as a potential behavioural marker predicting of therapy outcome and prognosis. These results may indicate that integrating the assessments of eating behavior may assist to individualise GLP-1RA treatment and enhance outcomes in clinical arenas [33]. Disparate inordinate Glucagon-like peptide-1 (GLP-1) receptor agonists are approved by the FDA for weight loss in obesity, essentially through targeting gastrointestinal pathways to diminish caloric intake; but there is limited information on the GLP-1 receptor agonist effect on the behavioural spheres of eating. On the whole, these findings suggest that GLP-1 receptor agonists promote extensive weight loss through perspicuously enhanced eating behavior regulation undergirding a condition whereby physiological cues highly influence behaviour

regarding food intake than sensory, [34] psychological, extraneous, and conditional cues.

Spheres of Glucagon-like peptide-1 receptor agonists and neurodegenerative diseases

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) moved from glucose-lowering agents to transformative therapies through several organ systems. GLP-1 RAs have depicted pleiotropic effects across primordial cellular mechanisms, such as enhanced mitochondrial functionality, anti-inflammatory actions, progressive cellular quality control, and comprehensive metabolic control. Determined applications exhibited robust efficacy in the management of diabetes (HbA1c decrements of 1.5–2.0%), treatment of obesity (weight loss of 7–24%), and cardiovascular preservation (14–20% decrement in principal hazardous cardiovascular events, or MACE. Emerging usage cut across neurological impairments, dermatological diseases, respiratory perturbations, and novel introductions in addiction medicine and autoimmune diseases. GLP-1 RAs constitutes a paradigmatic shift for multifaceted therapeutic intervention, with expansive evidence undergirding their functionality as overall metabolic modulators [8]. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are approved novel medications for diabetes and obesity as well as recognized significant scientific revelations. In combination with their metabolic impacts, these medications function on other pathophysiological [35] systems of several neurological and psychiatric dysfunctionalities. It becomes necessary to undertake research for the repurposing potential of GLP-1RAs in cognitive and mental aberrations, and advocacy for proper investigation and assessment of their safety inclination in a neuropsychiatric perspective [36, 37]. Although, semaglutide is approved for type 2 diabetes mellitus (T2DM), and investigated as a therapeutic regimen in brain perturbations, there are concerns on the emergence of deleterious neuropsychiatric incidents. Additional exploratory data are required for the assessment of the resultant impact of semaglutide on brain health [38]. There is no extant correlation between semaglutide and higher 12-month risk of hazardous neuropsychiatric outcomes in comparison to extraneous antidiabetic therapeutic considerations.

The interactions of metformin, type 2 diabetes and neurological impairment

Type 2 diabetes (T2D) increases dementia risk from 1.5 to 2.5 times. Sodium-glucose cotransporter 2 inhibitors (SGLT2is) and metformin are highly consumed antidiabetic treatment approaches which have shown potential neuroprotective impacts. Their comparative effectiveness in dementia prevention is not established. SGLT2is profoundly diminished dementia risk and mortality in contrast to metformin in T2D individuals. These suggest that SGLT2 is superior and neuroprotectively advantageous, undergirding its feasibility as a primordial therapy for T2D. Future



randomized trials are required to accent to these results or to confirm the findings [39].

Metformin is fundamentally a therapeutic drug for diabetes mellitus (DM), with additional clinical benefits encompassing more than glycemic control. It is not pellucid if the benefits of metformin extend beyond neurodegeneration prevention, for instance, in Alzheimer's disease (AD). Metformin was indicated to be significantly beneficial in the prevention of neurodegeneration, but has been ruled out as the optimal pharmacological agent of choice, especially in DM, when neurodegeneration is a fundamental concern in treatment decision-making with respect to other risk factors [40]. Type 2 diabetes mellitus (T2DM) is linked with an elevated risk of delirium and mortality. As glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are associated with metabolic and neuroprotective advantages, the long-term result on delirium risk is not pellucid. The usage of real-world data in comparison of GLP-1 RAs and metformin regarding delirium and mortality in T2DM patients demonstrated that GLP-1 RA application was at inception associated with a lower delirium risk, however, the association was later reversed due to probable subgroup variations in personalized therapy considerations. Metformin is considered a preferred option due to its consistent and reliable cognitive and survival advantages [41]. There are no strict comparisons which have assessed glucagon-like peptide-1 receptor agonists (GLP-1 RAs) against metformin as first-line antidiabetic treatment for dementia prevention type 2 diabetes mellitus (T2DM) individuals. A study conducted to assess the comparative effectivity of GLP-1 RAs and metformin in diminishing dementia risk showed that GLP-1 RAs depicted higher effectiveness than metformin in diminishing dementia risk, particularly AD and non-vascular varieties, exhibiting their potential as a prominent first-line therapy in T2DM. Extensive randomized trials are pertinent to validate these results [39].

Both glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and metformin have exhibited possible neuroprotective impacts in type 2 diabetes mellitus (T2DM), but no direct empirical comparisons have assessed the relative efficacies in impeding dementia. The large-scale, propensity score-matched cohort study depicts the significant diminished risk of total dementia by GLP-1 RAs, especially Alzheimer's disease and non-vascular dementias in contrast to metformin applied as first-line treatment in T2DM. It is suggested from these results that prompt application of GLP-1 RAs in T2DM patients at risk for cognitive decline influence future diabetes therapeutic guidelines to prioritize treatment with dual glycaemic and neuroprotective advantages [39]. The current study comparing and contrasting first-line therapies for type 2 diabetes unravelled that GLP-1 receptor agonists (RAs) correlated with a marked lower risk of the development

of dementia in comparison to metformin. Although, metformin provided a slight decrease in risk, GLP-1 RAs depicted a higher protective effect against Alzheimer's disease and other non-vascular dementias, specifically. These results are suggestive that GLP-1 RAs be given precedence in future therapy hierarchy in type 2 diabetes. However, further randomized trials are pertinent to confirm the outcomes.

Attendant sequelae of the coexistence of type 2 diabetes and cardiovascular disease

Coexistence or comorbidity of type 2 diabetes (T2DM) and cardiovascular disease (CVD) is commonplace with defined poor prognosis. Stringent and ardent risk factor regulation diminishes complication risks, however, treatment targets are unattainable, probably due to the complex and fragmented healthcare system as well as patient vulnerability. [42]. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) guarantee cardiovascular and renal therapeutic benefits for type 2 diabetes impairment but the real-world efficacy obesity without presenting diabetes are not decipherable. A study that evaluated the cardiovascular and hepatic responses of GLP-1RAs compared to any other anti-obesity medications (AOMs) in obesity adults GLP-1RA usage was proportionate to decreased cardiovascular, hepatic, mortality, and mental health risks in comparison to other AOMs [43]. An investigation of the COORDINATE-Diabetes trial indicated that a coordinated, multidimensional intervention substantially enhanced the quality of care for type 2 diabetes (T2D) and cardiac disease. This strategy embracing the unravelling of challenges in local prescription and provision in real-time feedback to clinics culminated in a significant augmentation in prescribing evidence-based medications, for instance, high-intensity statins, ACEIs/ARBs, and SGLT2 inhibitors/GLP-1 RAs) in contrast to formal or conventional care. Although, bereft of statistical significance, there was resultant trend of more depreciating outcomes, suggesting the coordinated model improve health equity and care for underserved [44], vulnerable and susceptible populations. Cardiac cachexia (CC) is an untoward and perilous heart failure (HF), with features of involuntary weight and muscle dissipation resulting in depreciating outcomes and elevated morbidity and mortality. Despite its deleterious characterisations, CC is barely given cognizance as an ailment that deserves proper therapy, management and specific pathophysiologic focus. Although, glucagon-like peptide-1 receptor agonists (GLP-1RAs) are worthy in the decrement of cardiovascular risk in HF patients, they may aggravate muscle dissipation in cachectic patients, prompting enhanced investigation activities. Non-pharmacologic approaches and targeted nutritional augmentation, physical training exercise are of contribute positive impacts on body composition and quality of life in CC patients. There are lacunae in targeted suggestions in preventative approaches and pharmacologic therapies for CC patients and attendant



and associated GLP-1RA usage. Studies on CC have explored the multifactorial processes underlying extant and emerging therapeutic measures for ameliorating HF-associated sarcopenia during GLP-1RAs use [45].

Meta analysis of GLP-1 receptor agonists in cardiovascular risk

A meta-regression analysis of GLP-1 receptor agonists incorporating the FLOW and SOUL trials detected that the decrement in cardiovascular risk correlates to the extent of HbA1c decelerating, but not bodyweight modification. It is indicated that HbA1c decrease can be useful as a substitute marker for the cardiovascular prognosis realised with GLP-1 RAs in type 2 diabetes persons, especially with the incorporation of a CKD-focused population and oral semaglutide data. [46]. HbA1c lowering, rather than bodyweight alteration, was significant and directly proportional to MACE risk lowering. A current bibliometric analysis demonstrated that global dulaglutide research (DGR) has manifested prominently with China, the United States, and the United Kingdom with Canada Canada presenting strengthened international collaboration. The research analysed data extending from 2010 to 2023 applying VOSviewer and Bibliometrix for the identification of pivotal study areas unravelling the structure of dulaglutide in cardiovascular disease, diabetes and obesity [47] DGR is an accelerating growing sphere with dynamic priorities from encompassing diabetes management to specified pharmacological and clinical disciplines. The propensity for the research underscores geopolitically the gaps and intellectual challenges, issues and opportunities of Dulaglutide research in future investigations and clinical applications and presentations. At a one-year follow-up of the real-world investigation of Asian Indians presenting with Type 2 Diabetes detected that respectively, glipizide monotherapy and glipizide-metformin combination therapy eminently enhanced HbA1c, fasting plasma glucose (FPG), and postprandial glucose (PPG). The combination therapy depicted greater effectivity in glycemic control improvement and fair body weight enhancement, whereas there were no prominent weight alterations in glipizide monotherapy. The two therapies established cost-effectiveness and preservation of β -cell functionality as observed from stable C-peptide levels, while glipizide and metformin coupling, not manifesting as an encumbrance, especially for developing nations [48]. These countries generally offer prescription sulfonylureas for cost-effectiveness. The collated data comparing and contrasting their real-world impact may be anecdotal or elusive, particularly when utilized as a monotherapy in contrast to pairing with metformin. Glipizide used as alone or combined with metformin, extensively enhanced glycemic regulation even in persons presenting with decelerating renal function, with no deleterious impacts on weight, preservation of β -cell function and general wellbeing. Inasmuch as protracted investigations are pertinent for the assessment and sustainability of these advantages,

outcomes and prognosis, glipizide is ostensibly a T2D cost-effective therapeutic alternative in developing nations. Double and triple incretin-based agonists, targeting coupled GLP-1, GIP, and glucagon receptors are newfangled strategies in the management of T2DM. Comparative efficacy and safety analyses streamlined to receptor-specific approaches are however restricted in certain systematic review and network meta-analysis which uniquely evaluate the efficacy and safety of double and triple incretin agonists in comparative analyses to conventional treatments with insights into individualized receptor-specific T2DM care. Receptor-specific targeting augments and improves T2DM therapy, with Semaglutide undergirding glycemic regulation, Tirzepatide promoting weight dissipation and glucose control, with the potential provision of Retatrutide for greater metabolic outcomes, enhancing receptor-targeted, and individualized treatment regimen [49].

Emerging and evolving medication-specific research

Novel medications and strategies are being developed to target the processes responsible for the deteriorating loss of skeletal muscle, such as ActRIIA and ActRIIB receptors dual blockade, wherein the research sphere is rapidly evolving. Glucagon-like peptide 1 (GLP-1) receptor agonists retard food intake, causing pronounced weight loss in overweight and obese persons. Although, a vast proportion of this weight loss involves fat mass, there is also incorporation of lean mass loss, in similarity to other mechanisms which induce deficit of calories. The targeting of signaling pathways which regulate skeletal muscle hypertrophy is a prognostic trajectory for the preservation of lean mass and to modulate body composition. Myostatin and Activin A are TGF β -like ligands which signal through the activin type II receptors (ActRII) to aggravate muscle growth. Pre-clinical and clinical studies promulgate that ActRII blockade triggers skeletal muscle hypertrophy and decline of fat mass [50]. To evaluate the adherence level to glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy utilising real-world data and to study the sociodemographic and clinical attributes related to GLP-1RAs discontinuation [51]. Approximately 20% of the patients discontinued GLP-1RA therapy within the initial year, whereas 50% was adherent. On the whole, lower socioeconomic status and higher comorbidity encumbrance were directly proportional to higher risk of discontinuing GLP-1RA treatment.

Globally, there is extensive medical significance and salience of skeletal muscle mass in humans [3, 52]. The vital functions of skeletal muscles are present in the public domain due to easy access to information on the impact of GLP-1 receptor agonists pertaining adverse weight loss. Research indicts the usage of these medications in skeletal muscle loss as highlighted by decrement in fat-free mass [FFM] which statistically range from 25% to 39% of the total mass dissipated in a



period of 36–72 weeks [53]. The remarkable muscle loss is suggestively attributable to the extent of weight loss contrary to the independent effect of GLP-1 receptor agonists. Future study is pertinent to unravel this hypothesis. In comparison, studies of non-pharmacological caloric restriction with reduced extent of weight loss lead to circa 10–30% FFM losses [54]. Contextually, the decrement in muscle mass with GLP-1 receptor agonists annually is more expansive in magnitude than could be predicted on an annual basis from age-correlated muscle loss (0.8% annually based on 8% muscle dissipation per decade within age 40–70 years). It is important to take into constant cognizance of muscle loss for clinicians, patients and vulnerable individuals to be increasingly aware of skeletal muscle and its prominence in health concerns as not to deviate from adherence and prioritisation of treatment and optimum prognosis.

The dissipation of weight via the use of GLP-1 drugs, such as semaglutide (Ozempic) may result in grave muscle loss, whereby accelerated weight loss can culminate in more expansive muscle mass dissipation than retarded weight loss. Decreased muscle mass relates with decrement in immunity, elevated infection risk, wound healing depreciation and decrement in survival rate. GLP1 receptor agonist therapies affect muscle by inducing pronounced weight dissipation, of which circa 40% of the dissipated weight is predominantly, lean muscle mass. Clinical trials have demonstrated that GLP-1 agonist drugs, such as semaglutide (Ozempic) tend to result in about 13.9% lean muscle mass loss [55]. GLP-1 drugs such as semaglutide (Ozempic) are aetiologic in lean muscle mass loss, with possibly culminating in attenuated immunity, elevated infection risk, and excoriated survival rates. Despite that one of the principal advantages of GLP-1 agonists is weight loss, investigation evidenced a significant aspect of the weight pertains to lean mass. Irrespective of these, resistance training, adequate protein intake, and aerobics contribute to the minimisation of muscle loss in GLP-1 treatment [56].

DISCUSSION

GLP-1 therapies have altered diabetes and obesity treatment, however, with the potential to elevate muscle loss risk. Newfangled GLP-1 treatments are being developed for improvement of the quality of weight and stem loss of skeletal muscle mass by better muscle mass preservation [3, 57, 58]. Recent investigations, such as the BELIEVE Phase 2b trial, have demonstrated that through the combination of a GLP-1 receptor agonist (semaglutide) [59] and bimagrumab, a drug targeting muscle loss, there can be enhanced body composition via decrement in fat with concomitant retention of muscle increment. This strategy intends to diminish the excess muscle loss that may associate with GLP-1-induced weight decrement, an extant issue with these

formidable weight-loss therapies. Pharmacological weight loss from glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and combined medications are tending towards the extent achieved with surgical interventions. With the achievement of increased weight loss, thereby provoking the concerns for potential deranging consequences on muscle abundance, quality, composition, and functionality [60]. Glucagon-like peptide-1 receptor agonists act by appetite suppression and caloric restriction. These therapies can lead to prominent muscle loss, ostensibly emanating from evolutionary processes shielding against food scarcity since muscle constitutes a principal energy consumer. A mechanism that attenuates muscle mass is activation of type II activin receptors (ActRIIA/B) which produce outstanding muscle growth in Man when blocked. An exhibition of GDF8 (myostatin) and activin A are both main ActRIIA/B ligands which mediate the minimization of muscle. Furthermore, dual blockade can stem muscle dissipation associated with glucagon-like peptide-1 receptor agonists coupled with proliferation of muscle mass in both obese mice and non-human primates. The muscle preservation augments fat dissipation and is of metabolic benefit. These data ascribe the potential that the supplement of glucagon-like peptide-1 receptor agonist therapy with GDF8 and activin A blockade may enhance the quality of weight loss in human obesity therapy [25].

This article overviews the pertinence to determine muscle-associated alterations related to weight loss therapies such as GLP-1 RAs can be maladaptive, adaptive or may potentiate response to weight loss following therapy. Investigations based on magnetic resonance imaging indicated that skeletal muscle alterations due to GLP-1 RA therapies are ostensibly adaptive (modifications in muscle volume z-score depict modifications in muscle volume which are proportional to predicted stances taking ageing into cognizance disease status, weight loss, insulin sensitivity improvement [61, 62] and muscle fat infiltration contribute to an adaptive process and progressively improved muscle quality and functionally, and lowering the potential for loss in power, prowess and functionality. Advanced age and prefrailty are factors which may attribute to appropriate selection of drugs due to sarcopenia risk [3]. GLP-1 receptor agonists (GLP-1RAs) are evolving cardiometabolic care via type 2 diabetes and obesity treatment, providing extra benefits, such as cardiovascular and kidney shielding. Evident challenges encompass side effects, particularly gastrointestinal issues, exorbitant costs of these medications, restricted access, potential weight recompense and lean mass loss following discontinuance. Future opportunities incorporate exploring newfangled double/triple agonists, oral formulations, nascent indications, for instance, nonalcoholic steatohepatitis (NASH) [3] and neurodegenerative disorders, concomitantly with optimization strategies for long-run advantages,



investigate or evaluate accessibility and pecuniary cost issues [63]. In order to sustain or improve muscle mass streamlined in combination with GLP-1-based therapies for patient-centered treatment optimization, focus on increasingly precise, accurate, meaningful, objective and holistic strategies [64, 65] for assessment of muscle health encompassing quantity, composition, function, mobility, and power are vital for the inordinate numbers of patients who may be indulged in the medications [66, 67] in the future. A prime significant aspect of this article is the comprehensive overview it characterises of GLP-1 receptor agonists, featuring multifaceted roles in the management of degenerative chronic conditions. The exposition of the glucagon-like peptides encompass: GIP and GLP-1 which are both gastrointestinal incretin hormones with complementary functionalities. Dual GIP/GLP-1 receptor agonists (RAs) exert higher potency than unadulterated GLP-1 RAs. Tirzepatide is a unimolecular GIP/GLP-1RA with usage in type 2 diabetes induces dose-dependent decrement in HbA1c and body weight. The tolerance of tirzepatide is closely similar comparable to the GLP-1RAs. Tirzepatide research is incessantly conducted in cardiovascular and liver disorders as well as obesity (MAFLD) [68, 69] with propensity for ardent medical research for the future [70].

Recommendation

This entry attempts to explore the expanding functionalities and therapeutic concerns of GLP-1 receptor agonists, with specific focus on the impact regarding muscle mass and chronic disorders. It delves into the duality of benefits and challenges posed by GLP-1 therapies, providing insights into associated therapeutic approaches and future research trajectories. This topic is pertinent given the increasing global prevalence of obesity and related metabolic aberrations. A novel sphere for GLP-1 receptor agonists (GLP-1RAs) essentially connotes the expanding arena of these drugs, embracing single, dual, and triple agonists which target GLP-1, GIP and glucagon receptors, with provision for enhanced therapeutic outcomes and prognosis beyond glucose control and weight loss. Aetiologically, GLP-1RAs attend to metabolic dysregulation via better insulin secretion, retarded gastric emptying, and appetite suppression. Therapeutic benefits for obesity, cardiovascular disease, chronic kidney disease, and non-alcoholic steatohepatitis (MASH) are unravelling with ardent and incessant research towards impacts on neurodegenerative states and substance use dysfunctionalities. The article provides an ardent spatiotemporal investigation and assessment into the dualistic characterisation of GLP-1 therapeutics in both ostensibly potential benefits and risks. The equilibration is vital given the broad consumption of the medications in disparate aspects of medicine. However, this could be ardently accommodated within extant academic discourse through an exploration of academic nuanced ambient of the gaps in current knowledge and for extensive

systematic evaluation of research findings. Succinctly put, this work presents a significant contribution by exploring the emergent landscape of GLP-1 therapies, and unveils the requisite equilibration of therapeutic benefits and concomitant risks and sequelae, essentially in muscle mass preservation. It remains a special reference point for clinicians, pharmaceutical interests and researchers to elucidate contemporary and future trends of GLP-1 therapies in chronic disorder management. Extensive studies on Tirzepatide for cardiovascular diseases and metabolic-associated steatotic liver disease (MASLD) are ongoing based on its approved usages for type 2 diabetes and obesity. Research is making advances in its mechanisms, effectivity, and potentialities regards its safety, reduced invasive substitute to surgery for these untoward anomalies, depicting excelling outcomes or prognosis per diminished liver fat, improved metabolic markers, mitigated risk of hepatic and cardiac sequelae. The review addresses a critical issue regarding the potential adverse impacts on muscle mass, with contribution to relevant insights of the polemics within the medical and pharmaceutical milieux. Moreover, the pertinence in defining protective modalities regarding protein intake and resistance training highlights holistic strategic patient care either in pro forma or strategic ambiguity arenas. Furthermore, it addresses future directions, suggesting an active effort to promote resilience in extant research and innovation in this regard.

CONCLUSION

The article considers the developmental spheres of GLP-1 drugs, from their incipient exposure via clinical applications, expressing evolving varied GLP-1 therapies concomitantly with the explicit pharmacological attributes. Also, the article articulates the potential usage of GLP-1 receptor agonists (GLP-1RAs) in disciplines such as neuropreservation, anti-infection modalities, the mitigation of variations of inflammation, and the potency of cardiovascular functionality. It offers an in-depth evaluation and monitoring of the affectivity of GLP-1RAs transversing pluralistic anatomic and physiologic systems which inculcate the nervous, cardiovascular, musculoskeletal, and digestive spheres via the integration of novel clinical trial data with penetration into potentialities of signaling pathways and pharmacologic processes. This review examines the expanding functionalities of GLP-1 therapies, efficacy evaluations in contrast to alternative or other treatments, emerging indications, current challenges, issues, opportunities and future directions. This review explores certain current spheres of medical dilemma with evolving and emerging risk assessment approaches critical for safe, compliant medical and recent updates on inter alia glucagon-like peptide-1 receptor agonists and impacts which incorporate sustainable future emphasis on therapy characterization, and risk-based evaluations in neurological diseases, muscle anomalies, sarcopenia,



cardiovascular diseases, diabetes, obesity and other chronic and noncommunicable disorders. Researchers tend to bring unrivalled expertise to ensure risk assessments are rigorous, regulatory-ready, and aligned with the newest international standards as depicted in this overview as Glucagon-like peptide-1 (GLP-1) drugs are inextricably-linked with appreciable muscle dissipation extending up to a third of overall weight loss. Although, it is assiduously being studied, it is a frequent concern due to the concomitant accelerated weight loss. The dissipation can be ameliorated by ardent consumption of high-protein diets in association with regular resistance exercise. Drugs which are associated with weight loss do produce muscle wasting. Inasmuch as the indicted drugs effectively induce weight dissipation, the application or strategy for healthy weight management prognosis is controversial. Specific concerns pertain that GLP-1 agonists are likely to be the aetiological agent in the dissipation of muscle mass, morphology and functionality. The dissipation of muscle mass, morphology and functionality is characterised in the elderly as sarcopenia. However, these effects become attenuated on discontinuance of GLP-1 and GIP related drugs, and the concomitant decrement in GLP-1/GIP receptor agonist activity following treatment interruption may result in weight recompensation. GLP-1 therapeutic medications have altered diabetes and obesity management, although, there may resultant concomitant exacerbated risk of muscle dissipation. The article addresses future directions for an active effort to promote resilience in extant research and innovation for Glucagon-like peptide-1 receptor antagonists in health and disease.

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