UC DAVIS
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for Food and Health

THE SCIENCE OF METABOLIC HORMONES: PRECISION NUTRITION IN THE "OZEMPIC ERA"

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CONTENT

EXECUTIVE SUMMARY

Metabolic hormones such as glucagon-like peptide-1 (GLP-1s), glucose-dependent insulinotropic polypeptide (GIPs) and others are transforming the way we treat obesity, type 2 diabetes, related metabolic dysfunctions and more. Originally developed to improve blood sugar control, GLP-1-based medications and other multi-agonists now demonstrate powerful effects on appetite regulation, weight loss, glucose control, cardiovascular protection, liver function, addiction and even brain health.

As GLP-1-based therapies profoundly shape how the body digests, absorbs, and responds to food, precision nutrition is emerging as an essential partner not only in supporting weight loss, but as a tool to impact hormone action, retain lean body mass, reduce side effects, and support long-term metabolic outcomes.

This white paper explores the science at the intersection of metabolic hormones and precision nutrition. It traces the discovery of incretin biology and the rise of multi-target therapies like tirzepatide (GLP-1 + GIP) and retatrutide (GLP-1 + GIP + glucagon), and shows how their widespread effects across brain, adipose tissue, muscle, bone, and the microbiome open new opportunities for nutritional intervention.

Key themes include:

- How dietary strategies – such as meal composition, timing, and targeted fiber intake – can be leveraged to support gut health, enhance gut hormone activity and reduce GI side effects.

- How lean mass and nutrient status be preserved during rapid weight loss through optimized protein quality, micronutrient intake, meal timing and resistance training.

- How tailored nutrition plans can help sustain results when pharmacological appetite suppression wanes.

We also explore the future of this field, including:

- Digital tools like continuous glucose monitors (CGMs), wearables, and AI-driven dietary platforms for real-time feedback and support.

- Smart delivery systems for GLP-1 based medications, including oral and tissue-targeted formulations.

- The challenges of long-term tolerance, receptor desensitization, and how nutrition may help buffer or mitigate these effects.

These next-generation GLP-1-based therapies, combined with the power of nutrition, represent a paradigm shift in metabolic care. By moving beyond a one-size-fits-all approach, we can offer more effective treatments that not only deliver greater weight loss and metabolic improvements but also enhance adherence and quality of life. Ultimately, the future of this field lies in integrating these cutting-edge therapies with personalized, data-driven strategies – from digital tools and AI platforms to dietary recommendations and next-generation drug and food formulations – to create a holistic and sustainable path to better health.

INTRODUCTION

The global rise in type 2 diabetes, obesity and metabolic dysfunction has accelerated demand for treatments that go beyond calorie restriction and blood sugar control. For decades, therapeutic strategies focused primarily on lifestyle modification or so-called “diet drugs,” (eg; amphetamines, fenfluramine) many of which proved addictive or unsafe. Even with the advent of glucose-lowering medications such as sulfonylureas and later metformin, the focus remained largely on controlling blood sugar rather than addressing the broader, systemic drivers of metabolic disease. The emergence of GLP-1 receptor agonists (GLP-1RAs) and multi-agonist therapies has disrupted that paradigm.

But as these therapies become more widespread, a new question has emerged: How can food and nutrition be leveraged to support and optimize their effects? While pharmacologic agents can shift hormonal signaling and alter physiology, what we eat – and how we eat – remains essential to sustain optimal body functions. The rise of GLP-1–based and multi-agonist therapies has created new opportunities and new challenges for dietary intervention.

GLP-1-based therapies reshape appetite regulation, digestion, nutrient absorption, and energy balance, meaning that nutrition itself must evolve to work in synergy. We are now entering a new phase of care in which strategic approaches to nutrition are not just a complement to pharmacotherapy, but a critical co-driver of treatment success moving beyond generic dietary recommendations. It involves tailoring macronutrient and micronutrient composition, meal timing, food quality, and microbiome support to align with an individual’s physiology and treatment response.

This white paper explores the interplay between GLP-1-based therapies and nutrition, and how dietary strategies can improve both the effectiveness and tolerability of these medications. From the foundational science behind metabolic hormone biology to emerging insights into the gut microbiome, appetite regulation, and tissue-specific hormone actions, the goal is to clarify how GLP-1-based therapies and nutrition together shape metabolic outcomes – and how precision approaches can help unlock their full potential.

METABOLIC HORMONES AND THE EMERGENCE OF MULTI-TARGET METABOLIC THERAPIES

Discovery of Incretins and the Foundations of Gut-Derived Pharmacology

The development of modern therapies for metabolic diseases traces back to the discovery of gut-derived hormones – known as incretins – that potentiate insulin secretion in response to nutrient intake. In the 1960s, researchers observed that oral glucose ingestion provoked a stronger insulin response than intravenous glucose administration, a phenomenon described as the "incretin effect." [1], [2]. This observation suggested that something beyond blood glucose was at play and that the gut was acting as a metabolic command center releasing hormones that amplified the insulin response to help the body manage blood sugar more efficiently after meals.

Two key hormones behind this effect were subsequently identified.

- GIP (glucose-dependent insulinotropic polypeptide) [3], [4], secreted from K-cells in the upper small intestine

- GLP-1 (glucagon-like peptide-1) [5], [6], secreted from L-cells in the lower intestine (ileum and colon)

Both hormones work in a glucose-dependent manner - in response to nutrient intakes - enhancing insulin secretion only when blood sugar is elevated, a safety feature that prevents hypoglycemia [7], [8]. Of the two, GLP-1 stood out due to its broader physiological actions, which include stimulation of insulin release, suppression of glucagon (a hormone that raises blood sugar), delayed gastric emptying, and reduced appetite [7], [8], [9].

With the recognition that these gut-derived hormones could modulate multiple aspects of postprandial (post-meal) metabolism, a new question

emerged: could these be harnessed as antidiabetic agents? The primary obstacle was their stability. Despite playing a key role in regulating glucose after meals, incretin hormones are rapidly degraded in the blood within minutes by the enzyme dipeptidyl peptidase-4 (DPP-4), limiting their therapeutic potential [10].

To overcome this, two strategies were developed:

- Build stronger synthetic versions of GLP-1 engineered to resist degradation and act longer in the body. These compounds are known as the GLP-1 receptor agonists (GLP-1 RAs) such as liraglutide and semaglutide – the active compounds in Victoza® and Ozempic® [11], [12], [13].

- Develop oral medications that block the enzyme responsible for breaking down natural GLP-1 and prolonging their activity. These drugs, like Sitagliptin, are known as DPP-4 inhibitors [14].

While both classes were initially approved for glucose control in type 2 diabetes (T2D), GLP-1 RAs have since demonstrated superior efficacy and additional benefits compared to DPP-4 inhibitors, including clinically meaningful weight loss and reductions in cardiovascular risk [15], [16]. This broadened their relevance to the management of metabolic disorders. Importantly, they fundamentally change how people experience food: slowing gastric emptying and motility, reducing appetite, and altering tolerance for meal size, fat, and fiber. This means rethinking how food is designed, portioned, and prepared – whether packaged food, home cooked meals, or meals consumed at restaurants. Consumers taking these drugs need smaller, nutrient-dense servings that are easier to digest and deliver essential nutrition in ways that align with their new physiological needs.

Expanding the Metabolic Toolbox: Toward Multi-Agonist Therapies

While GLP-1 receptor agonists rapidly advanced to clinical success, other hormones are now reshaping the therapeutic landscape. GIP, originally dismissed because its insulin-stimulating effects seemed blunted in type

2 diabetes [17], has proven far more versatile when paired with GLP-1. In combination, GIP may enhance insulin sensitivity, improve fat metabolism, complement GLP-1 action on appetite pathways in the brain [18], [19]. It also helps fine-tune glucagon secretion — supporting glucose stability by preventing excessive suppression, while at the same time amplifying glucagon's beneficial roles in fat burning and energy expenditure. Notably, it helps offset some of the gastrointestinal side effects (nausea) associated with GLP-1RAs, contributing to the improved tolerability of dual GIP/GLP-1 therapies [20]. This shift in understanding paved the way for the development of tirzepatide, a dual GIP and GLP-1RA known as Mounjaro® and Zepbound®, respectively, approved for T2D and obesity. In clinical trials, tirzepatide produced outcomes that exceeded expectations:

- Superior glycemic control compared to GLP-1 monotherapy [21].
- Significant weight reduction, often exceeding 20% of body weight [22].
- Promising cardiovascular and kidney protective effects [23], [24].

Attention is now turning to a broader set of metabolic hormones that extend the therapeutic reach beyond glycemic control.

Glucagon: An Emerging Therapeutic Ally

Glucagon is an essential hormone predominantly secreted in the pancreas that complements insulin by mobilizing glucose from the liver when energy is needed [25][24]. Beyond this well-known role in glucose regulation, recent research highlights its broader contributions to metabolism, particularly its ability to:

- Promote the breakdown of stored fat (lipolysis) [26].
- Increase energy expenditure [27].

- Stimulate heat production through fat burning (thermogenesis), especially in brown and beige fat [28].

- Promote insulin secretion [25].

These properties make glucagon an attractive addition to weight-loss therapies when balanced with GLP-1 or GIP agonism. Although GLP-1 drugs lower blood sugar by suppressing glucagon, adding glucagon back in a controlled way can actually boost fat burning and energy use, making combination therapies more efficient. This is exemplified by investigational agents like retatrutide, a triple agonist targeting GLP-1, GIP, and glucagon receptors simultaneously. Early trials suggest that this combination may deliver greater reductions in body weight and fat mass than dual agonists alone, while also improving glycemic control and lipid metabolism [29].

Amylin: A Satiety Hormone

Amylin is co-secreted with insulin by pancreatic β-cells and plays an important role in postprandial glucose regulation and appetite suppression [30]. Its key actions include:

- Slowing gastric emptying, which delays nutrient absorption and prolongs satiety [31].

- Suppressing post-meal glucagon release, thereby improving glucose control [32].

- Acting centrally to reduce food intake by promoting satiety signals in the brain [33].

Although pramlintide, a synthetic amylin analog, was approved for diabetes over a decade ago, its adoption was limited as it required an injection with every meal and often produced gastrointestinal side effects [34]. However,

amylin is now being revisited through newer, better-tolerated analogs and co-formulated therapies. A prime example is CagriSema, which combines semaglutide (GLP-1 RA) with cagrilintide, a long-acting amylin analog, now in final-stage trials (Phase 3), with FDA approval expected in 2027. This combination is designed to enhance satiety and weight reduction, while also smoothing postprandial glycemic spikes. Both animal and early clinical data indicate that GLP-1 and amylin agonism may synergize to enhance appetite regulation and fat loss, potentially exceeding the effects of GLP-1 alone [30], [35], [36].

Additional formulations under investigation also include new hybrid molecules that combine metabolic hormones with other therapeutic agents to simultaneously target multiple tissues and pathways. For example, fusing GLP-1 with FGF21 – a liver hormone involved in lipid metabolism – may offer synergistic benefits for obesity-related liver disease known as metabolic dysfunction-associated steatotic liver disease (MASLD) [37], [38]. Similarly, amylin – estrogen conjugates are being investigated for their ability to reverse metabolic syndrome in animal models [39].

Together, these innovations reflect a shift toward poly-agonist therapies (see Table 1) that deliver synergistic effects on weight loss and metabolic health by boosting energy expenditure and strengthening satiety signals. The greater efficiency of these combinations means they can also be used at lower doses resulting in fewer side effects. At the same time, this new physiology creates nutritional challenges: greater need for nutrient-rich foods despite reduced overall intake. Patients on these therapies will require smaller, protein-rich, nutrient-dense meals that preserve lean mass, ensure adequacy, and support long-term metabolic health even when appetite is diminished.

Drug Name (Brand name)	Target Receptors	Status	Primary Indication
Tirzepatide (Mounjaro®, Zepbound®)	GLP-1 + GIP	FDA-approved	Type 2 Diabetes, Obesity/Overweight
Mazdutide	GLP-1 + Glucagon	Approved in China, in clinical trials elsewhere	Obesity/Overweight, Type 2 Diabetes
Survodutide	GLP-1 + Glucagon	Phase 3 Clinical Trials	Obesity/Overweight, MASH
Pemvidutide	GLP-1 + Glucagon	Phase 2 Clinical Trials	Obesity/Overweight, MASH
Retatrutide	GLP-1 + GIP + Glucagon	Phase 3 Clinical Trials	Obesity/Overweight, Type 2 Diabetes, MASH
Cagrilintide/ Semaglutide (CagriSema®)	GLP-1 + Amylin	Phase 3 Clinical Trials	Obesity/Overweight, Type 2 Diabetes

Table 1. Summary table of GLP-1-based multi-agonists approved or under clinical trial.

MASH: Metabolic dysfunction-associated steatohepatitis (A type of liver disease caused by fat buildup and inflammation, usually linked to obesity and diabetes).

MULTISYSTEM PHYSIOLOGY OF METABOLIC HORMONES

Metabolic hormones such as GLP-1, GIP, glucagon, PYY3-36 and amylin operate far beyond the pancreas. Naturally secreted after meals, they signal through receptors located in the gut, brain, adipose tissue, muscle, and bone – creating widespread systemic effects [40]. Pharmacologic analogs and receptor agonists act on the same pathways though with longer-lasting and more pronounced effects, amplifying their influence on how the body processes and responds to food. Understanding these multisystem interactions is key to optimizing therapy, predicting outcomes, minimizing unintended side effects and even expanding indication to other pathologies. Notably, these therapies both influence and are influenced by nutrition, making dietary strategies an integral component of pharmaceutical-based care.

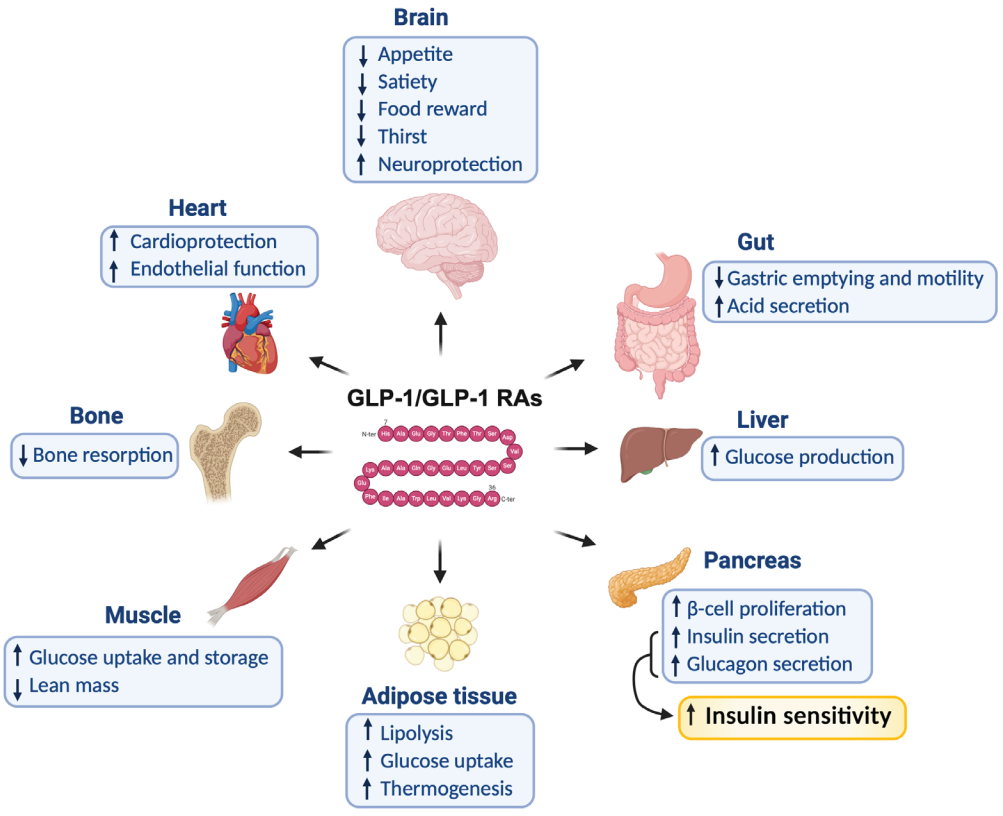

Figure 1. Effects of GLP-1 and GLP-1 Receptor Agonists on multiple organs. Adapted from [41].

Gut and Microbiota

The gut hosts trillions of microbes that strongly shape how we process food and regulate metabolism. These microbes affect nutrient absorption, blood sugar control, energy storage, and inflammation [42], [43], [44]. When this community is imbalanced – a state called dysbiosis – it has been linked to obesity, insulin resistance, and type 2 diabetes [45], [46], [47]. Importantly, nutrition is a strong driver of this balance: diets high in fiber and microbiota-accessible carbohydrates (the types of carbohydrates we can't break down but that gut microbes can digest and use for energy), found in legumes, beans, nuts, seeds and whole-grain products tend to support a healthier microbiome, while diets rich in processed foods, high in refined sugars, saturated fat, food additives including colorants, emulsifiers (blending agents), artificial sweeteners (eg; Saccharin) and low in fiber are more likely to create imbalance [48], [49], [50].

The relationship between gut microbes and naturally secreted incretin hormones works in both directions. On one side, microbes break down dietary fiber into short-chain fatty acids (SCFAs: acetate, propionate, butyrate). These compounds stimulate GLP-1 and PYY3-36 release, support satiety, improve insulin sensitivity, lower inflammation, and help maintain the gut barrier [51], [52], [53], [54]. On the other side, GLP-1 and GIP hormones feed back on the gut by slowing motility and changing fermentation patterns, which in turn reshapes microbial communities [55], [56]. This two-way interaction suggests that GLP-1–based therapies may not only regulate appetite and glucose control directly, but also shape the gut microbial environment in ways that reinforce these effects, potentially improving overall treatment efficacy.

Certain microbial species associated with SCFA production, such as *Faecalibacterium prausnitzii, Akkermansia muciniphila,* and *Bifidobacteria*, have been linked to improved metabolic profiles and are thought to support the body's own GLP-1 secretion and action [57], [58], [59], [60]. Conversely,

animal models have shown that disrupting the microbiome with antibiotics can impair GLP-1 secretion and reduce postprandial hormone responses [61], [62], [63].

Beyond SCFAs, microbial secondary metabolites – including indole derivatives from tryptophan metabolism and bile acid derivatives – may further modulate GLP-1 release, receptor expression, or downstream metabolic signaling [62], [64], [65].

Although non-digestible dietary fibers, complex carbs, as well as prebiotics, and probiotics supplements show promise in improving gut microbial diversity and function, clinical evidence that they directly enhance GLP-1-based treatment outcomes remains limited [66]. Moving forward, future research must clarify which fiber types and doses are most effective, whether specific probiotic strains reliably augment incretin signaling, and how microbiome profiling can explain patient variability and guide more personalized nutrition strategies [67], [68].

Metabolic Hormones and the Brain

Metabolic hormones – like GLP-1, GIP, amylin, glucagon and PYY3-36 – play an important role in regulating appetite, not just by acting in the digestive system, but also by signaling directly to the brain. These signals influence satiety, thirst, how much we eat, and even how rewarding we find certain foods (hedonic eating) [69], [70].

These hormones reach the brain through two main routes:

- Some travel through the **bloodstream**, reaching areas of the brain that monitor metabolic signals.
- Others communicate via the **vagus nerve**, a direct line between the gut and brainstem.

GLP-1 is naturally produced not only in the gut but also in specific regions of the brain and in pancreatic islet alpha-cells where it exerts local action to enhance insulin secretion [71], [72]. After a meal, GLP-1 released in the gut enters the bloodstream where it normally helps regulate blood sugar, slow digestion, and reduce hunger [73]. In the brain, it strengthens feelings of fullness and reduces appetite by enhancing satiety signals [74]. Drugs that activate GLP-1 receptors amplify these effects, leading to stronger reductions in appetite and blunting the brain's response to high-calorie food cues.

Emerging research extends this role into addiction pathways. Pharmacological activation of GLP-1 receptors appears to reduce alcohol intake in preclinical models and early human studies, possibly by dampening reward signaling in the brain [75], [76]. This suggests GLP-1–based therapies may influence not only food cravings but also substance use, highlighting a broader role for these drugs in regulating reward-driven behavior.

Interestingly, GLP-1 has also been detected in taste buds [77], [78], [79], suggesting it may directly influence flavor perception and help explain the reduced appeal for sweet or high-calorie foods seen among people on GLP-1 drugs. Reinforcing this shift in food preference with nutrient-dense food while minimizing caloric load can support long-term behavior change toward healthier dietary habits.

Another important effect is on hydration and thirst regulation. GLP-1 receptor agonists appear to alter thirst perception and may interact with hormones such as arginine vasopressin (AVP), which regulate fluid balance [80], [81], [82]. Many patients on GLP-1 medications report reduced thirst [83], raising the risk of chronic dehydration and highlighting the need for targeted hydration solutions — such as fortified low-calorie beverages or electrolyte-enhanced products — designed for individuals with blunted thirst signals.

Beyond GLP-1, several other gut-derived hormones influence brain circuits that regulate appetite and food choice. While traditionally viewed as a gut hormone, GIP is now recognized to act on the brain, influencing appetite and energy balance both when naturally secreted and through therapeutic agonists [84]. Recent studies suggest that GIP may also have neuroprotective effects with preclinical work indicating that pharmacological activation of GIP receptors can reduce neuroinflammation, improve synaptic function, and enhance neuronal survival [85]. These findings have sparked interest in GIP analogs as potential therapies for neurodegenerative diseases such as Alzheimer's and Parkinson's, although clinical evidence in humans is still limited. Amylin, released alongside insulin from the pancreas, also acts on the brain (specifically the area postrema) to reduce meal size and slow digestion, reinforcing satiety [86]. PYY3-36, another gut-derived hormone released after eating, similarly activates satiety pathways in the hypothalamus and brainstem, partly via activation of the vagus nerve [87], [88].

Collectively, these hormones recalibrate major brain regions – including the hypothalamus, brainstem and reward circuits – that regulate hunger, satiety, and decision-making around food (including reduced grocery spending) [89], [90], [91]. Understanding how metabolic hormones engage with the brain helps explain why pharmacological interventions – particularly multi-agonist therapies – can lead to meaningful behavioral changes, enabling individuals to eat smaller meals and shift preferences away from highly processed, energy-dense foods. As research continues to map these brain–gut hormone pathways, this creates new opportunities to develop foods that align with these altered preferences—providing essential nutrients in smaller portions while reinforcing healthier dietary patterns to support long-term metabolic health.

Adipose Tissue

Adipose tissue – more commonly known as body fat – is not just a passive energy store. It functions as an active endocrine organ, releasing hormones including leptin and adiponectin which help regulate food intake, energy balance, insulin sensitivity, thermoregulation, and immune responses [92], [93].

Importantly, not all fat is the same.

- **White adipose tissue** (WAT) or white fat stores excess energy and makes up the majority of fat in the body.

- **Brown adipose tissue** (BAT) burns energy to produce heat and is more metabolically active.

- **Beige adipose tissue**, found within white fat, can be activated under certain conditions (like cold exposure or hormonal signals) to behave like brown fat and contribute to energy expenditure [93], [94], [95].

Naturally, metabolic hormones including GLP-1, GIP, glucagon, and amylin act directly on fat tissue, influencing whether fat is stored or mobilized and how efficiently the body can use these reserves for energy [28], [94], [96]. Clinical evidence shows that GLP-1 receptor agonists and newer multi-agonist therapies extend these signals, leading to stronger reduction in total white fat. This impact is greatest on visceral fat, a key contributor to metabolic diseases [97], [98]. These therapies not only lower total body fat but also shift fat distribution toward a healthier profile. For instance, some multi-agonists may improve lipid metabolism by promoting the “browning” of WAT into beige fat, enhancing energy expenditure and fat oxidation [96]. These changes in fat distribution are accompanied by improvements in blood lipid profiles: lower triglycerides, reductions in LDL-cholesterol, and in some studies modest increases in HDL-cholesterol [96], [97].

In obesity, adipose tissue function is further compromised by chronic low-grade inflammation. This is driven by changes in immune cells populations within fat tissue – specifically, an increase in pro-inflammatory cells and a reduction in protective immune cells. Together, these shifts worsen insulin resistance and limit the tissue's ability to adapt and function properly [99].

This is where precision nutrition comes into play. As highlighted in recent research, targeted dietary strategies can reduce inflammation in fat tissue, promote thermogenesis, improve fat-derived hormone levels, and enhance sensitivity to metabolic hormones [100]. For example, healthy dietary fat (omega-3 fatty acids, monounsaturated fat), polyphenols, and dietary fibers have been shown to improve insulin sensitivity and reduce inflammation – partly by restoring adiponectin levels or improving leptin and insulin signaling [101]. Some food compounds such as caffeine or capsaicin (the spicy compound in chili pepper) may complement the effects of GLP-1 based therapy on energy expenditure by promoting an increase in BAT thermogenesis [102]. By combining GLP-1 based therapies with personalized nutritional approaches, it may be possible to restore healthier fat tissue function, lower inflammation, and improve long-term metabolic outcomes in individuals with obesity or insulin resistance.

Metabolic Hormones and Musculoskeletal Health

Muscle and bone are not just structural tissues–they also play important roles in how the body uses and stored energy [103]. As research evolves, it's becoming clear that these tissues are not only influenced by metabolic hormones but also release factors that shape whole-body metabolism and should be considered part of the broader picture in obesity and diabetes treatment [104]. Nutrition adds a critical layer here: by supplying adequate protein, micronutrients, and functional bioactives, diet can help preserve muscle and bone, optimize their endocrine functions, and complement the benefits of GLP-1-based therapies .

Skeletal Muscle: A Major Metabolic Organ

Skeletal muscle is the largest site of glucose uptake in the body and a major contributor to how many calories we burn at rest. Keeping muscle healthy is key for insulin sensitivity, physical strength, and overall metabolic health. Naturally secreted GLP-1 and GIP may improve insulin sensitivity and glucose uptake in muscle tissue via indirect signaling [40]. However, rapid weight loss with GLP-1 and related medications can include some lean mass loss – typically 15–25% of the total weight lost. While body composition generally improves overall, preserving muscle is important to maintain metabolic rate, strength, and long-term weight stability once treatment stops [105]. Emerging evidence suggests that multi-agonist therapies—particularly those including amylin or combining anabolic signals – may help spare lean mass more effectively than GLP-1 monotherapy, though more research is needed to confirm these effects [106], [107].

In addition to responding to circulating metabolic hormones, skeletal muscle also acts as an endocrine organ by releasing factors such as irisin, IL-6, and FGF21 that influence energy metabolism, inflammation, insulin sensitivity, and cross-talk with adipose tissue, liver, and brain [108]. These effects are particularly relevant in the context of obesity and diabetes, where muscle-derived signaling plays a key role in maintaining whole-body metabolic balance.

As such, strategies to maintain or restore muscle function – through pharmacological, nutritional, and/or exercise-based interventions – are increasingly viewed as important components of metabolic disease management. Importantly, preserving muscle during weight loss through nutritional strategies is becoming a key priority in the development of multi-agonists therapies – not only to support metabolic health but also to maintain physical function, particularly in aging populations.

Bone: Hormonal Regulation and Metabolic Cross-Talk

Bone is also metabolically active, with receptors for hormones like GIP and GLP-1 that may influence bone formation and quality. Some evidence suggests that naturally secreted GIP may promote bone density, while GLP-1 appears to have indirect, protective effects on bone by modulating calcium balance and reducing bone resorption in animal models [109], [110], [111].

By contrast, the effects of GLP-1 receptor agonist (GLP-1 RA) medications on bone are less clear with human studies showing mixed results [112]. During the rapid weight loss induced by GLP-1 RAs nutrient intake often drops – leading to potential deficits in bone-supporting micronutrients that can reduce bone mineral density. Mitigating this risk is particularly important in populations vulnerable to bone loss, such as older adults or postmenopausal women at risk for osteopenia [113].

Nutritional strategies to protect muscle and bone during weight loss therapy should prioritize high-quality protein in adequate amounts (1.2–2 g/kg of body mass/day [114]) evenly distributed across meals along with key bone-supporting nutrients (calcium, vitamin D, magnesium…) delivered in smaller, nutrient-dense portions adapted to reduced appetite. Since individual needs vary, these principles should be paired with dietary assessment to guide meal planning or supplementation that matches personal requirements and deficiencies.

Cardiovascular system

In addition to regulating glucose, appetite, and fat metabolism, metabolic hormones – particularly GLP-1 – play an important role in cardiovascular health [115]. This is especially relevant for people with obesity or type 2 diabetes, who face a significantly elevated risk of heart disease and stroke.

GLP-1 receptors are widely distributed, including in the heart, blood vessels, kidneys, and brain, suggesting that GLP-1RAs and multi-agonists may influence cardiovascular function through multiple pathways [115], [116].

This has been confirmed in multiple large-scale clinical trials [117] (such as LEADER, SUSTAIN-6, and REWIND), which showed that GLP-1RAs :

- Reduce the risk of major cardiovascular events, including heart attack and stroke
- Improve blood pressure and lipid profiles
- Reduce inflammation and enhance endothelial function

As a result, several GLP-1 RAs – including liraglutide (Victoza®), dulaglutide (Trulicity®), and semaglutide (Ozempic®/Wegovy®) – have been approved specifically for cardiovascular risk reduction in people with type 2 diabetes and high cardiovascular risk [118].

In addition to GLP-1, other metabolic hormones are now being explored for their cardiovascular potential. GIP and Glucagon agonists when combined with GLP-1-RAs may enhance lipid metabolism and reduce inflammation, potentially amplifying cardiovascular benefits [119]. Amylin agonists, particularly in combination with GLP-1-RA, may contribute to improved postprandial lipid control and modest reductions in blood pressure [120]. This new wave of therapies – including multi-agonists that combine GLP-1, GIP, and glucagon receptor activation – are now in advanced clinical trials. Agents like tirzepatide or retatrutide are being investigated not only for weight and glucose control, but also for cardiovascular outcomes.

Together, these findings reinforce the concept that GLP-1-based therapies may offer meaningful cardiovascular protection, positioning them as a cornerstone of future cardiometabolic care. Nutritional strategies can complement these effects through the development of food products enriched with omega-3 fatty acids (EPA/DHA, algal oils), polyphenol-rich extracts (olive, grape, cocoa), and plant sterols and soluble fibers (eg; psyllium and β-glucan found in oats, barley, mushrooms, nutritional yeast), which collectively improve lipid profiles, support endothelial function, and reduce inflammation [121], [122], [123].

TAILORED NUTRITION IN THE OZEMPIC ERA

While hundreds of reviews and articles outline dietary recommendations for obesity, diabetes, and cardiometabolic health, a significant knowledge gap remains on how these guidelines should be adapted for people using GLP-1–based and multi-agonist therapies. Nutrition must be tailored at each stage of the therapy – early on to manage side effects, during maintenance to preserve lean mass and prevent deficiencies, and after discontinuation to address changes in nutritional needs associated with metabolic rebound. By altering appetite, digestion, energy expenditure, and metabolic signaling, these medications profoundly influence the body's response to food, meaning that traditional "healthy diet" advice may not fully address the unique nutritional challenges they create. Yet, studies directly examining how nutrient absorption, mobilization and availability shift under different GLP-1 RA treatments remain scarce. Addressing these questions will create opportunities to develop more precise nutritional strategies that align with pharmacological treatment to optimize therapeutic response, minimize side effects, and support long-term health outcomes.

Dietary management is not simply about calorie restriction. It requires strategic adaptation of meal composition, timing, and structure to match individual physiological changes induced by these therapies. These medications are known to reduce appetite, delay gastric emptying, and alter gut motility. While beneficial for weight loss, such changes can lead to inadequate nutrient intake, gastro-intestinal discomfort, or reduced meal tolerance if not properly managed.

A phase-specific nutritional strategy can help mitigate these effects. During initiation, smaller, more frequent meals that are low in fat and fiber are often better tolerated and reduce nausea. Over time, nutrient quality

becomes critical. Prioritizing a variety of high-quality proteins rich in leucine along with supplementation of the leucine metabolite Beta-Hydroxy-Beta-Methylbutyrate (HMB) and creatine in combination with resistance exercise, can help preserve functional tissues including lean muscle mass, especially during periods of rapid weight loss [123], [124], [125]. Maintaining hydration and electrolyte balance is also essential, as GLP-1 therapies can blunt thirst perception. This reduced fluid intake may increase the risk of dehydration and micronutrient imbalances, underscoring the need for strategies that support adequate hydration [80], [83], [126]. Ultimately, personalized plans that evolve across treatment phases, with clinical support, are more likely to improve adherence, tolerability, and sustained therapeutic success.

Evidence shows that patients on GLP-1 therapies often fall below benchmarks for key nutrients – including vitamins B12, D, folate; minerals such as magnesium, zinc, and iron; and phytonutrients like carotenoids and flavonoids [125], [127]. Left unaddressed, these deficiencies may contribute to fatigue, anemia, cognitive changes, and impaired immunity – not only undermining the long-term success of treatment but potentially resulting in adverse clinical outcomes [124]. Food formulations designed for reduced appetites must therefore deliver micronutrient density in smaller portions. In addition, regular screening for micronutrient deficiencies could help identify individual gaps, allowing for personalized meal planning and targeted supplementation to support patients on metabolic therapies.

Beyond composition, the structure of food such as particle size, fiber content, and processing can influence glycemic response by modifying gastric emptying and nutrient absorption [128], [129]. For example, finely ground foods are digested more quickly, leading to a faster glucose rise, while larger particles (like whole grains or minimally processed foods) slow digestion and flatten the glycemic curve. Innovation in food formulations that work synergistically with slowed digestion may improve tolerance, glycemic control, and support sustained satiety despite reduced overall intake during therapy.

Another emerging area of interest is the influence of gut microbiome on both hormone activity and treatment response. Dietary fibers (e.g., inulin, resistant starch) and targeted probiotics (e.g., Lactobacillus rhamnosus GG, Bifidobacterium animalis) can promote short-chain fatty acid (SCFA) production, enhance GLP-1 secretion, improve insulin sensitivity and reduce gut inflammation – potentially amplifying the therapeutic effects of GLP-1 RAs [57], [58], [62], [130]. However, these fibers should be introduced gradually to avoid bloating or GI discomfort, especially during the early weeks of therapy.

Nutrition also plays a key role when weight loss plateaus or treatment is discontinued. As appetite returns and metabolic adaptations emerge, tailored dietary strategies that sustain nutrient quality, manage energy density, and preserve lean mass become critical to preventing weight regain [131].

Importantly, individual factors – such as baseline muscle mass, dietary habits, GI tolerance, microbiota composition and genetic predisposition – should guide nutritional adjustments. Recent evidence highlights that some people perform better than others in assimilating certain food and nutrients according to their metabolic capacity (metabotypes) [132], [133], [134]. Metabotype profiling can therefore help predict individual response to dietary intervention and further guide precision approaches.

Ultimately, as GLP-1 RAs reshape obesity and diabetes care, nutrition must evolve in parallel—not only to facilitate weight loss, but to ensure broader and more durable improvements in metabolic health.

CHALLENGES AND FUTURE DIRECTIONS

Despite remarkable advances in GLP-1 RA therapies for obesity and metabolic disease, important challenges remain. As the field moves toward more personalized, poly-hormonal, and digitally integrated approaches, three priorities stand out: ensuring long-term safety, sustaining therapeutic efficacy, and improving real-world implementation.

Digital and AI-Driven Support

The rise of continuous glucose monitors (CGMs), wearable trackers, and nutrition apps has created new opportunities for real-time assessment on how diet, physical activity, and medication influence one another [135]. These tools can help patients better understand how their food choices and activity patterns intersect with pharmacotherapy, improving adherence and outcomes.

Looking ahead, AI-driven platforms will play a key role in personalizing nutrition and medication timing based on an individual's rhythms, hormone responses, and lifestyle factors [136]. Emerging systems that combine CGM data with AI are being explored alongside GLP-1 therapy to guide meal composition and portioning, which may help stabilize glucose responses and enable more personalized nutrition strategies [137]. In parallel, advances in AI are also being used to better characterize the molecular composition of food, moving beyond macronutrient content to analyze thousands of bioactive compounds and their interactions with human biology [138], [139]. AI-powered food databases and modeling tools can help predict how specific foods or nutrients influence hormone signaling, inflammation, or microbiome composition, laying the groundwork for more precise, individualized dietary recommendations that complement

pharmacological therapies [140], [141]. The future lies in integrated platforms that combine wearables with genetic information, microbiome profiles, food composition and behavioral inputs to deliver truly personalized care plans – potentially even adjusting medication dosing in real time.

Durability, Safety, and Next-Generation Drug Design

One major challenge for GLP-1-RA therapies is maintaining efficacy over time. Chronic receptor stimulation may lead to receptor desensitization and downregulation, raising concerns about reduced effectiveness with long-term use [142]. Strategies under investigation include intermittent dosing, drug cycling, and combining agents that act through complementary pathways to sustain sensitivity [143], [144]. Safety also remains a key question, especially in non-diabetic populations, with ongoing studies assessing effects on cognition, fertility, thyroid function, bone health, and the consequences of sustained weight loss on lean mass and reproductive hormones [111], [145], [146], [147], [148]. Closing these knowledge gaps will be critical to ensure the safe, lifelong use of these therapies in broader patient populations.

To address these challenges, the next wave of therapeutic innovation is focused on increasing precision, enhancing delivery, and broadening applicability. One promising approach is the use of biased agonists, which are designed to preferentially engage signaling pathways that maintain metabolic benefits. Although this approach may offer sustained efficacy by limiting receptor downregulation, whether biased agonists also reduce side effects such as nausea remains to be confirmed [149], [150]. Future research advancing our understanding of tissue-specific and context-dependent GLP-1 receptor signaling will be essential to unlock the next wave of therapeutics that combine superior efficacy with improved safety [151].

Improving drug delivery remains a key focus in the development of next-generation GLP-1–based therapies. While current formulations are predominantly injectable, several innovative approaches are being pursued

to reduce treatment burden and improve long-term adherence. These include ultralong-acting injectables that extend dosing intervals, implantable devices that enable continuous and controlled hormone release, and smart delivery systems such as electronic injectors or wearable pumps that can automate administration based on physiological cues [152].

In addition, noninvasive alternatives – including oral, inhaled, and emerging small-molecule GLP-1 receptor agonists – are being developed to improve convenience and accessibility [144]. Notably, unlike oral peptide GLP-1 RAs (Rybelsus®), which must be taken on an empty stomach with water at least 30 minutes before eating or other medications, small-molecule candidates such as orforglipron (a GLP-1 medication currently in clinical trials) can be taken once daily without food or water restrictions. This food-independent dosing simplifies use, may improve adherence, and could broaden access to GLP-1 therapies.

More futuristic strategies, such as nutrient-inducible cell therapies, demonstrate how drug delivery could be synchronized with meals. In preclinical studies, scientists engineered implantable cell capsules that sense dietary cues such as caffeine and release GLP-1 only when triggered. In mice, this approach improved post-meal blood sugar control by matching hormone release directly to food intake [152], [153]. Although still experimental, these approaches illustrate the potential for therapies that align pharmacologic action with nutrient intake, potentially improving efficacy while reducing treatment burden and side effects.

Ultimately the future of GLP-1-based medications lies in pairing advanced drug design and delivery with precision nutrition and digital tools to deliver safer, longer-lasting metabolic health.

CONCLUSION

The landscape of metabolic care is undergoing a profound transformation, moving beyond single-target drugs to a synergistic, multi-hormone approach that engages the body's complex hormonal networks. This shift, driven by the success of next-generation therapies like dual and triple agonists, reflects a growing recognition that metabolic health is not regulated by one isolated system, but by coordinated interactions across the gut, brain, adipose tissue, muscle, liver, and beyond. While these therapies have demonstrated significant clinical benefits, their effectiveness is not determined by pharmacology alone. A range of individual factors – including dietary patterns, body composition, microbiota diversity and microbe metabolism, and genetic background – can influence treatment response, tolerability, and long-term outcomes. Addressing this variability is an important step in optimizing the use of GLP-1-based and multi-agonists therapies for individuals.

In this context, precision nutrition plays a central role. It moves beyond general dietary recommendations by aligning nutritional intake–including macronutrient distribution, meal timing, and microbiome-targeted strategies–with the physiological and therapeutic needs of the individual. With recent estimates revealing that one in eight U.S. adults have used GLP-1 medications, the food industry is adapting – reformulating products into smaller, nutrient-dense portions and introducing 'GLP-1–friendly' claims to align with reduced appetites and new nutritional needs. To drive real impact, this trend must be backed by clear standards, science-based evidence, and transparency so it can evolve into a meaningful wave of food innovation that supports healthier long-term eating habits.

Looking ahead, the integration of pharmacology, personalized nutrition, and emerging data technologies is expected to support more individualized approaches to metabolic care. Advances in multi-omics technologies–

including genomics, proteomics, and metabolomics – are beginning to offer more detailed insights into the biological variability that shapes treatment outcomes. These tools may help move nutritional strategies beyond broad dietary guidelines toward more specific, adaptive recommendations that reflect a patient's hormonal responses, microbiome composition, and genetic predispositions.

Importantly, these technologies are also contributing to a deeper understanding of food itself–not only as a source of nutrients but as a complex matrix of bioactive compounds that can influence metabolic processes, immune function, and hormone signaling. This knowledge may enable the development of more targeted dietary strategies. For instance, identifying an individual's gut microbial profile could inform the use of specific prebiotics or probiotics to support endogenous GLP-1 activity, mitigate medication side effects and improve therapeutic response.

Ultimately, the future of metabolic therapy will rely on the coordinated application of pharmacology, individualized nutrition, and real-time biological data collection to better address the complexity and variability of human metabolism.

CONTRIBUTORS

Antoine Abrieux
Strategic Research Associate, Innovation Institute for Food and Health

Sean Adams
Professor & Vice Chair for Basic Research, UC Davis School of Medicine

Kirstie Canene Adams
Director of Nutrition, Ingredion

Dana Armstrong
Talent Development Coordinator, Innovation Institute for Food and Health

Mary Avilla
Program Manager, Innovation Institute for Food and Health

Mariana Barboza
Research Program Manager, Innovation Institute for Food and Health

Kate Chartrand
Head of Brand Communications, AG1

Bethany Cummings
Professor, UC Davis School of Medicine

Ralph Esposito
Chief Science & Nutrition Officer, AG1

Kim Fisher
Director of Programs, Innovation Institute for Food and Health

Mariana Barboza
Research Program Manager, Innovation Institute for Food and Health

Rene Herrera
Program Assistant, Innovation Institute for Food and Health

Veronica Keys
Program Assistant, Innovation Institute for Food and Health

Laura Kunces
Senior Director of Scientific Affairs, AG1

Lara Nyman
Vice President of Research and Discovery, AG1

Marissa Pickard
Strategic Marketing Manager, Innovation Institute for Food and Health

Justin B. Siegel
Associate Professor of Chemistry, Biochemistry & Molecular Medicine, UC Davis | Faculty Director, Innovation Institute for Food and Health

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