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PERSPECTIVE ARTICLE

State-of-the-art perspective: Advances in incretin-based therapy targeting progression of diabetes and cardiovascular-kidney-metabolic syndrome

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Abstract

The incretin system is targeted in the treatment of type 2 diabetes mellitus (T2DM) and cardiovascular-kidney-metabolic (CKM) conditions. Increasingly, incretin hormones (i.e., gut peptides that enhance glucose-stimulated insulin secretion) reduce blood glucose levels, consequently alleviating CKM syndrome. Specifically, glucagon-like peptide 1 (GLP-1) demonstrated glucose-lowering effects, delayed gastric emptying, decreased glucagon secretion, and weight loss. An investigational medication, retatrutide, interacts as a tri-agonist with glucose-dependent insulinotropic polypeptide (GIP), GLP-1, and the glucagon receptor. Contemporary data indicate that early intervention, targeting not only the GLP-1 receptor but also the GIP and glucagon receptors, are forthcoming therapeutics affecting T2DM in earlier phases and CKM outcomes, demonstrating the advances in tri-agonists versus only GLP-1. Notably, endogenous levels of gut incretin hormones shift as pre-diabetes progresses to diabetes or regresses to normoglycemia. The present perspective provides a review of incretin therapy and its prospects in hindering the progression of T2DM and CKM syndrome.

Keywords: Pre-diabetes; Type 2 diabetes; Cardiovascular-kidney-metabolic syndrome; Incretin mimetics; Obesity

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1. Introduction

Incretin-based therapies have revolutionized the treatment of type 2 diabetes mellitus (T2DM) and cardiovascular-kidney-metabolic (CKM) conditions. These therapies target the incretin system, which involves gut peptides that enhance glucose-stimulated insulin secretion, thereby reducing blood glucose levels and alleviating CKM syndrome.[20,21] Glucagon-like peptide-1 (GLP-1) has emerged as a key player in this therapeutic approach. GLP-1 receptor agonists demonstrate multiple beneficial

effects, including glucose-lowering effects, delayed gastric emptying, decreased glucagon secretion, and weight loss.[26-29] These culminating effects make GLP-1 receptor agonists powerful tools for controlling blood glucose and improving CKM syndrome.

Notably, endogenous levels of gut incretin hormones shift as prediabetes progresses to diabetes or regresses to normoglycemia.[23] This dynamic nature of incretin hormone levels underscores the potential benefits of early intervention with incretin-based therapies. Recently, multi-agonist approaches have been developed, particularly the combination of GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptor activation.[34] This tri-agonist approach, exemplified by investigational medications like retatrutide, aims to provide enhanced therapeutic benefits compared to GLP-1 receptor agonists alone. Early clinical data suggest that these tri-agonists may offer superior efficacy in weight reduction and glycemic control compared to selective GLP-1 receptor agonists.[35] Contemporary research indicates that early intervention with incretin-based therapies may be crucial in hindering the progression of T2DM and CKM syndrome. Targeting not only the GLP-1 receptor but also the GIP and glucagon receptors in earlier phases of the disease could potentially lead to better outcomes.

As the development of incretin-based therapies continue to evolve, additional research has been focused upon optimizing the balance between GLP-1, GIP, and glucagon receptor activation, developing long-acting formulations for improved patient compliance, and investigating potential applications beyond T2DM, such as in neurodegenerative optic disease and metabolic dysfunction-associated steatohepatitis.[21,41] Thus, incretin-based therapies offer a promising approach to targeting the progression of diabetes and CKM syndrome, with potential benefits extending beyond glycemic control to address the broader spectrum of metabolic disorders.

2. Impact of pre-diabetes and diabetes in the United States

In 2021, diabetes was the eighth leading cause of mortality in the United States (U.S.), with 103,294 death certificates documenting diabetes as the underlying cause of death (crude rate: 31.1/100,000 people).[1] Among the U.S. population in 2021, the crude estimate for diabetes was 38.4 million people across all ages (11.6% of the U.S. population).[1] Furthermore, in 2022, the total direct and indirect estimated costs of diagnosed diabetes in the U.S. was $413 billion.[2] Besides diabetes being a leading cause of mortality globally, it is also a leading cause of disability worldwide, accounting for 26.8%.[3] Based upon the National Diabetes Statistics Report from the Centers for Disease Control and Prevention, an estimated 97.6 million adults aged 18 years or older had pre-diabetes (38.0% of the adult U.S. population) in 2021. Moreover, 27.2 million people aged 65 years or older (48.8%) had pre-diabetes.[1] These data demonstrate the significant public health impact of the potential progression of those with pre-diabetes to overt diabetes.

A new American Heart Association (AHA) presidential advisory identified the strong connections between cardiovascular disease (CVD), kidney disease, type 2 diabetes mellitus (T2DM), and obesity, defining cardiovascular-kidney-metabolic (CKM) syndrome.[4] As the pre-cursor to diabetes, pre-diabetes is the earlier phase of the toxic CKM cascade of diabetes. Pre-diabetes is clinically diagnosed with glycated hemoglobin (hemoglobin A1C) or dysglycemia levels.[5] According to the American Diabetes Association, pre-diabetes can be defined by the following:[5]

(i) Hemoglobin A1C: 5.7 – 6.4%
(ii) Fasting blood glucose: 100 – 125 mg/dL
(iii) Oral glucose tolerance test 2-h blood glucose: 140 – 199 mg/dL

The pathophysiology of pre-diabetes involves dysglycemia with increased insulin production and overstimulation of pancreatic β-cells, with diminished insulin receptor response over time. Consequently, if pre-diabetes is unabated, insulin resistance, insulin hypersecretion, and progression of pancreatic β-cell function decline will occur, resulting in T2DM. Ultimately, if left untreated, inflammatory responses stimulate both micro- (i.e., retina, kidney, and nerves) and macrovascular complications (i.e., cardiovascular [CV] system). The AHA recently developed an inclusive equation, Predicting Risk of Cardiovascular Disease Events (PREVENT), with clinical variables of obesity, diabetes, kidney disease, and social risk, thereby supporting a multicomponent concept for effectively and equitably enhancing CKM population health.[6] The PREVENT equation facilitates both 10- and 30-year risk estimates among adults at 30 – 79 years of age for total CVD and includes the estimated glomerular filtration rate as a predictor while adjusting for competing risk of non-CVD death. Ndumele *et al.*[4] provided a synopsis of new strategies and research aimed at improving CKM syndrome, focusing on CKM variables and their relation to where, when, and how to implement and disseminate the vast array of cardioprotective therapies for CKM. Recently, meta-analyses demonstrated that pre-diabetes is associated with the risk of mortality, diabetes-related complications, and CV comorbidities,[7] representing a continuum of risk for diabetes and eventual CKM.[5,8]

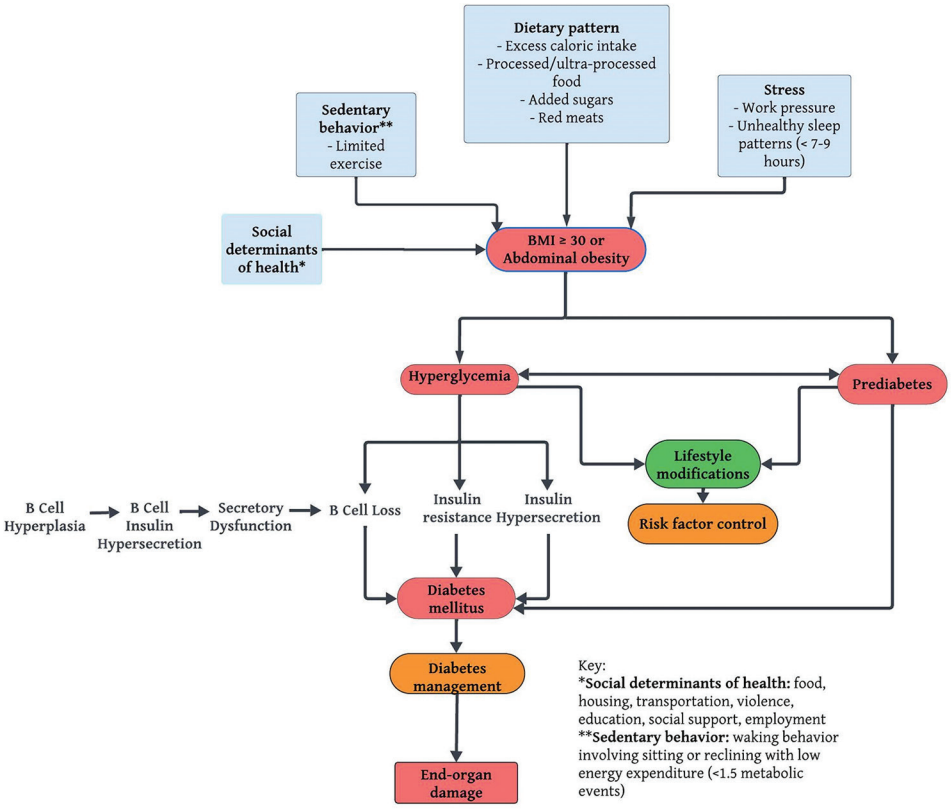

Figure 1. Progression of risk factors to diabetes mellitus and corresponding outcomes. Adapted from[10,16,17,18]

3. Addressing pre-diabetes, diabetes, and associated obesity

Of those who experience intermediate hyperglycemia or pre-diabetes, almost all of them will progress to T2DM.[9] Notably, there has been a striking increase in diabetes, rising from only 1% five decades ago to nearly 10% today.[10] Insulin resistance and genetic abnormalities are not independently responsible for this dramatic increase in diabetes. Conversely, obesity has been characteristically centered at the core of the crisis, with overweight and obesity noted as the most common risk factors associated with the development of T2DM.[10,11] As a major risk factor leading to the development of T2DM, obesity can lead to β-cell loss and dysfunction.[8] Biondi and colleagues[8] outlined the natural history of β-cell failure in obesity-induced T2DM, separating into successive steps beginning with β-cell compensatory hyperplasia and insulin hypersecretion, to insulin secretory dysfunction, and finally, loss of β-cell mass (Figure 1). Aligned with the chronic obesity-induced pathophysiologic changes leading to diabetes, at least a 5% weight reduction may result in a reversal of metabolic abnormalities and with additional weight loss, the potential to discontinue diabetic medications.[12]

Table 1. Mechanisms of incretin-based therapy in dysglycemia

Agent	Mechanism
GLP-1 receptor agonist	Binds to GLP-1 receptors on pancreatic B-cells, stimulating insulin, inhibiting glucagon release, slowing gastric emptying, and promoting satiety to improve blood glucose control
Dual GIP/GLP-1 receptor agonist	Binds to GLP-1 receptors (see above) and GIP receptors on pancreatic B-cells, enhancing insulin secretion, inhibiting glucagon release, and improving insulin sensitivity to regulate blood glucose levels
GIP-1/GLP-1/ glucagon receptor triagonist (retatrutide*)	GIP-1/GLP-1 agonist mechanism is similar to the above; glucagon receptor activation stimulates lipolysis, increases energy expenditure, prevents hypoglycemia, and balances glucose control effects when combined with GLP-1 and GIP agonists

Note: *Retatrutide is currently under investigation. Adapted from Jakubowska *et al.*[20]
Abbreviations: GLP: Glucagon-like peptide; GIP: Glucose-dependent insulinotropic polypeptide.

The cornerstone of pre-diabetes management is through lifestyle modification, with a focus on significant weight loss. A weight loss reduction of 5 – 7% has been demonstrated to be effective, typically achieved through a low-fat diet combined with an exercise regimen of about

30 min/day.[13] Therefore, proper management of pre-diabetes with specific lifestyle modifications is effective in preventing diabetes, thereby reducing the risk of CVD. Accordingly, the U.S. National Diabetes Prevention Program (DPP) integrates moderate weight loss (5 – 7%) through a healthy diet and physical activity over the course of a year for those with increased risk of diabetes or diagnosed with pre-diabetes.[13] The DPP is an evidence-based program that demonstrated a significant reduction in risk of developing T2DM by 58% (71% for people over 60 years old) after losing 5 – 7% of their body weight with healthier eating and 150 min of physical activity per week.[14] Moreover, surgical interventions (i.e., bariatric surgery) demonstrated beneficial outcomes, including improved glycemic control and weight reduction, in the treatment of pre-diabetes and T2DM.[15]

Although difficult to instill and maintain, lifestyle interventions, including diet and exercise, are considered first-line cornerstone treatments. As exemplified by the long-term follow-up of the original DPP study, the DPP outcomes study evaluates the effects of the interventions on diabetes complications, (i.e., retinopathy, microangiopathy, CVD). Accordingly, although the lifestyle group participants started off with the most weight loss (mean of 7 kg after 1 year), they gradually regained most of the weight.[5] Therefore, the need for medical therapy, in addition to lifestyle interventions, should be instilled and maintained as part of a toolbox of interventions. Pre-diabetes can be managed with two medications, metformin and acarbose; however, these are contraindicated among patients with renal disease.[15] A compounding challenge of pre-diabetes is its predominantly asymptomatic nature, which acts as a "silent incubator" for impending morbidity. As pre-diabetes develops into T2DM, medications also contribute significantly to controlling the toxic effects of hyperglycemia. Despite these evidence-based treatment options, tackling pre-diabetes is not fully targeted as a method to prevent the negative impacts of T2DM. Examining the mechanism of action and potential early targets of the newer incretin mimetics may expose the underutilization of these mechanisms to slow or potentially halt the progression of overt diabetes (Table 1). Given the abundant data conferring pre-diabetes as an increased risk for progression to T2DM and CKM syndrome, treatment should focus on preventing the progression to T2DM.[19]

Encouragingly, Glucagon-like peptide-1 (GLP-1) receptor agonists demonstrate a reduction in liver fat and consequently improve liver enzyme levels, thereby paving a treatment avenue for metabolic dysfunction-associated steatotic liver disease or the more advanced form, metabolic dysfunction-associated steatohepatitis (MASH), for which there is no Food and Drug Administration-approved treatment at this time.[21] Ongoing phase 3 trials aim to provide data that may support the development of effective pharmacotherapies for patients with MASH.[21] Accordingly, efocipegtrutide (HM15211), long-acting glucagon, Glucose-dependent insulinotropic polypeptide (GIP), and GLP-1 triple full agonist, is currently in the pipeline and undergoing a phase 2 randomized, multicenter 52-week study among patients with biopsy-confirmed non-alcoholic steatohepatitis.[22]

4. Targeting incretin response

Among healthy individuals, oral glucose stimulates greater insulin secretory responses than intravenous glucose, despite equivalent glucose levels. Food breakdown in the gut promotes the release of incretins (i.e., GIP and GLP-1), which enhance insulin release. Notably, this physiologic response (also known as the "incretin effect") in T2DM is markedly decreased or absent. The malfunction may be linked to the dysfunction of β-cells or a specific defect within the GIP signaling pathway.[23] Thus, a depressed incretin effect of GIP leads to an increase in post-prandial glucose levels, potentially worsening glycemic control. In contrast, GLP-1 is much less impaired than GIP in the setting of T2DM. The CKM outcomes of GLP-1 secondary to its glucose-lowering effects include a reduction in A1C (~0.8 – 1.6%), body weight (~1 – 3 kg), blood pressure, and lipids.[24,25]

In 2024, the landmark "Evaluate Renal Function with Semaglutide Once Weekly" trial reported findings of the first kidney outcomes trial evaluating the GLP-1 receptor agonist semaglutide.[26] Compared to those who received a placebo, participants with T2DM and chronic kidney disease who received semaglutide demonstrated a 24% risk reduction of the composite primary endpoint, including kidney outcomes and mortality secondary to CV and kidney causes.[26] Secondary endpoints include significant enhancements with semaglutide, slower estimated glomerular filtration rate slope, a decrease in major CV events (18%), and a reduced risk of all-cause death (20%). Notably, the reduction in kidney outcomes with semaglutide was consistent in participants with/without baseline sodium-glucose cotransporter-2 inhibitor (SGLT2i) use. A recent meta-analysis and systematic review of randomized controlled trials (RCTs) validated the long-term efficacy and safety of semaglutide compared to placebo in overweight/obese adults without diabetes. The once-weekly semaglutide dose was associated with decreased body weight and demonstrated beneficial effects on CV risk factors (i.e., body mass index, waist circumference, blood pressure), with limited mild-to-moderate gastrointestinal (GI) side effects.[27]

Since exogenous GLP-1 stimulates insulin, suppresses glucagon, and decreases plasma glucose concentrations

in both fasting and post-prandial states, the development of selective GLP-1 receptor agonists and co-agonists (i.e., stimulation of GIP and GLP-1 receptors) are the imminent therapeutic focus for early intervention of diabetes. Furthermore, in June 2024, a 1.8 mg liraglutide injection became the first generic GLP-1 approved in the U.S. for the treatment of T2DM.[28]

An example of the synergistic effects of GIP and GLP-1 includes the medication tirzepatide, which is an innovative treatment for T2DM classified as a dual agonist. Tirzepatide increases post-prandial insulin secretion, while concurrently inhibiting glucagon secretion. Moreover, tirzepatide enhances satiety through central (hypothalamus) and peripheral (slowing of gastric emptying) action, resulting in substantially improved glycemic control and weight reduction in T2DM.[29] Notably, tirzepatide has demonstrated a greater degree of engagement for the GIP receptor than the GLP-1 receptor, corroborating an imbalanced mechanism of action.[30] This supports its classification as an imbalanced dual GIP and GLP-1 receptor agonist. *Post hoc* analysis from the "Study of Tirzepatide in Participants with Type 2 Diabetes Not Controlled with Diet and Exercise Alone" (SURPASS) program indicated beneficial effects of tirzepatide with improvement in A1c, body weight, and cardiometabolic markers. These benefits were observed in participants with early-onset T2DM (<40 years of age), who, despite their younger age, demonstrated higher glycemic levels and lower metabolic health at baseline.[31] Recently, Malhotra *et al.*[32] completed a 52-week phase 3, double-blind RCT to evaluate the efficacy and safety of tirzepatide for the treatment of moderate to severe obstructive sleep apnea (OSA) in obese people. Of the 469 participants that were randomized 1:1 to receive tirzepatide or placebo, tirzepatide reduced moderate-to-severe OSA severity by up to 62.8%, which translates to 30 fewer events restricting or blocking a person's airflow per hour of sleep. In addition to reducing the hypoxic burden, tirzepatide also reduced body weight, high-sensitivity C-reactive protein concentration, and systolic blood pressure and enhanced sleep-related patient-reported outcomes.[32] Currently, tirzepatide is being investigated with dulaglutide to evaluate the CV protective outcomes in the "Effect of Tirzepatide Versus Dulaglutide on Major Adverse Cardiovascular Events" (SURPASS-CVOT) study in patients with T2DM (ClinicalTrials.gov: NCT04255433).[33]

In addition, a novel incretin mimetic under investigation is retatrutide, a GLP-1/GIP/glucagon receptor tri-agonist. Jastreboff *et al.*[34] completed a phase 2 RCT in 338 obese adults with retatrutide versus placebo over 48 weeks. At the maximum dosage of retatrutide (12 mg) and after 48 weeks, the average weight loss was 24.2% with a weight reduction of up to 30% from the baseline weight among 25% of participants. Notably, the weight reductions were accompanied by several encouraging CKM outcomes, including improved glycemic control among both fasting glucose and Hemoglobin A1C (HbA1c), decreased waist circumference, lower systolic and diastolic blood pressures, and lower lipid levels. The side effects and safety profile were similar to GIP/GLP-1 receptor co-agonists, with mild-to-moderate GI effects, which mostly occurred during dose escalations.[34] Importantly, the documented weight loss is the most significant through a pharmacological agent, and the mechanism of action is secondary to the GIP/GLP-1 receptor co-agonism complemented by the glucagon receptor activation and augmentation of energy intake.[35]

5. Potential side effects of incretin agonists in overweight and obesity

Although incretin agonists provide multiple beneficial impacts on CKM, including significant weight reduction of ~15 – 24% in adults with overweight and obesity, there is a concern for potential sarcopenia. Several trials have reported that about 25 – 40% of the weight loss was composed of fat-free mass (FFM)/lean body mass; however, obese people have greater amounts of FFM and skeletal muscle mass (SMM) than the lean population. The SMM is higher in obese people than in lean individuals, but the percentage of the SMM (compared to total body mass) is lower.

Intentional weight loss leads to a greater decrease in body fat than FFM or SMM, thus improving the ratio of FFM/SMM to fat mass and the quality of the remaining muscle.[31,36] Recent reports have demonstrated that appropriate counseling to mitigate this potential side effect includes maintaining a balanced diet rich in protein, ensuring adequate hydration, and engaging in regular physical activity with resistance training.[37,38] While achieving fat loss, Locatelli *et al.*[38] further proposed that resistance training should be integrated as an adjunct to incretin therapy to optimize changes in body composition, leading to the preservation of lean body mass. Although there is concern that significant weight loss induced by incretin mimetics can cause physical frailty or sarcopenia, there is currently no data to support this claim.[39]

In regards to the adverse effects of GLP-1 receptor agonists, GI effects are the most prevalent; however, these effects are dependent on agent potency and dose. The side effects include various upper GI (i.e., nausea, vomiting) and lower GI (i.e., diarrhea, constipation) symptoms. However, slower dose titration reduced these effects, and thus, the overall safety profile remains strong.[40] According

to an observational retrospective matched cohort study, semaglutide was associated with an increased risk of non-arteritic anterior ischemic optic neuropathy,[41] and future studies to assess causality were proposed. Well-designed trials powered for microvascular outcomes are warranted to clarify associations between incretin therapies and microvascular diseases.

Previous meta-analyses of RCTs suggested an association between the use of GLP-1 receptor agonists and retinopathy in patients with T2DM. However, conflicting results from additional studies challenge these findings.[42] According to a recent systematic review and meta-analysis of RCTs comparing the effect of SGLT-2i, GLP-1 receptor agonists, and dipeptidyl peptidase-4 inhibitors (DPP-4i) on the risk of diabetic retinopathy in patients with T2DM, Malyszczak and colleagues[42] highlighted the challenges in concluding that these newer antidiabetic drugs differ substantially in their effect on diabetic retinopathy complications. Currently, the data advises caution with the use of DPP-4 inhibitors and semaglutide, especially among patients with underlying retinopathy.

Given the innovative therapeutics being developed and studied for T2DM and obesity, the data support the implementation of these medications in clinical studies to potentially treat pre-diabetes and obesity early on as a preventative measure to halt the progression to overt T2DM. With the increasing prevalence of these co-morbidities and the frequent association of obesity with CKM syndrome, the effective weight loss and HbA1c reduction achieved with incretin mimetics may also benefit patients with pre-diabetes, offering cardioprotective and hepatic steatosis-reducing properties. Although the early results are encouraging, the mechanisms of action of incretin hormones on various organs and systems remain inconclusive.

Overall, incretin mimetics offer many positive effects to negate the progression of diabetes. Besides the glucose-lowering properties of incretin mimetic, both the reduction of appetite and food intake result in weight loss, thereby proposing a feasible mechanism of action for diabetes prevention. Although incretins' efficacy for weight loss and improvement in quality-of-life has been documented, there is a gap in evidence among patients with and without diabetes demonstrating a reduction in the risk of CVD in the intervention phase or during chronic follow-up care.[20,43,44]

6. Conclusion

Although both therapeutic and lifestyle interventions have demonstrated the benefit of reducing the incidence of T2DM, there remains a gap in understanding the impact of incretin mimetics in reducing CKM risk in pre-diabetic patients post-intervention. In addition, although lifestyle modification should be the cornerstone of therapy, innovative incretin therapeutics may have a significant impact, given the concurrent weight loss outcomes as well.

Incretin mimetics simulate the incretin hormone function to return blood glucose levels to the euglycemic range. More recently, a study demonstrated how endogenous levels of gut incretin hormones change as pre-diabetes advances to diabetes or regresses to normoglycemia.[45] Based on contemporary data, evidence indicates that early intervention, targeting not only the GLP-1 receptor but also the GIP and glucagon receptors, is imminent. Now is the time to implement and disseminate these therapeutics to tackle T2DM in its earlier phases, ensuring physiologic β-cell function and promoting weight reduction. Furthermore, these are therapeutic targets that could potentially be implemented in patients diagnosed with pre-diabetes to hinder the progression to T2DM. Most recently, the emerging benefits of GLP-1 receptor agonists, beyond glucose control, have reportedly impacted not only CKM conditions but OSA as well.[46] Shifting from sedentary habits and overnutrition to increased physical activity and reduced nutrient intake leads to weight loss, subsequent euglycemia, and improvements in CKM outcomes. Future research directions should focus on how incretin mimetics affect individualized responses to treatment of obesity and CKM syndrome by evaluating their interactions with endocrine cells, the nervous system, genetic makeup, and the composition and intake of nutrients.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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