STAR OF SCIENCES
MULTIDISCIPLINARY JOURNAL
ISSN:3091-1885
Vol. 2 Núm. 2 (2025) Revista Científica

Metabolic Revolution: Redefining Endocrinology with Novel Incretin-Based Therapies

Revolución metabólica: redefiniendo la endocrinología con nuevas terapias basadas en incretinas

Para citar este trabajo:
Ramírez Hernández , A. ., González Araujo , J. E. ., Ducoing Castillo , J. F. ., Azua Martínez, M. E. ., Zaga Cohen, N. E. ., Uriostegui Navarro, A. F. ., Navarro Chavez , M. A. ., & Longares Morales, A. L. . (2025). Revolución metabólica: redefiniendo la endocrinología con nuevas terapias basadas en incretinas. Star of Sciences Multidisciplinary Journal, 2(2), 1-22. https://doi.org/10.63969/tg610p62

Autores:

Alexis Ramírez Hernández
Universidad España
Durango - México
alexrmzhdz26@gmail.com
https://orcid.org/0009-0003-9877-4302

Nicole Esther Zaga Cohen
Universidad Westhill
Estado de México, México
nicolezaga3@gmail.com
https://orcid.org/0009-0005-9102-3391

José Enrique González Araujo
Universidad Autónoma de Chiapas
Chiapas, México
araujo261220@gmail.com
https://orcid.org/0009-0009-4386-4945

Alexa Fernanda Uriostegui Navarro
Universidad del Valle de Cuernavaca
Morelos - México
fernavarro0401@gmail.com
https://orcid.org/0009-0007-9161-3177

Jorge Fabián Ducoing Castillo
Universidad del bienestar Benito Juárez
Guanajuato- México
jorgeducoing38@gmail.com
https://orcid.org/0009-0004-9804-3515

Martín Alejandro Navarro Chavez
Universidad Autónoma de Guadalajara
Jalisco - México
martin.navarro.esspana.3@gmail.com
https://orcid.org/0000-0001-5200-7448

Martín Eduardo Azua Martínez
IMSS Centro Médico Nacional Siglo XXI
CDMX - Mexico
azua013@hotmail.com
https://orcid.org/0009-0002-6257-6921

Alondra Lizeth Longares Morales
Universidad del Valle de Cuernavaca
Morelos - México
alongares4@gmail.com
https://orcid.org/0009-0009-7348-9832

Autor de Correspondencia: Alexis Ramírez Hernández, alexrmzhdz26@gmail.com

RECIBIDO: 15-Septiembre-2025 **ACEPTADO**: 29-Septiembre-2025 **PUBLICADO**: 13-Octubre-2025

ISSN:3091-1885

Resumen

El presente estudio multinacional evaluó los efectos metabólicos, cardiovasculares, renales y hepáticos de las terapias basadas en incretinas en adultos con obesidad y diabetes mellitus tipo 2 (DM2) en México, Colombia y Ecuador. Tras 12 meses de tratamiento, los participantes mostraron mejoras consistentes y clínicamente significativas en todos los parámetros evaluados. El peso corporal disminuyó en promedio 10.7%, la HbA1c en 1.3 puntos porcentuales y la glucosa en ayuno en 23.5%, acompañadas de reducciones favorables en presión arterial y perfil lipídico. La tasa de filtrado glomerular estimada (eGFR) aumentó (+2.3 mL/min/1.73 m^2) y la albuminuria se redujo (−14 mg/g), evidenciando protección renal. Los parámetros hepáticos (ALT, CAP, FIB-4 y NFS) también mejoraron, indicando regresión de la esteatosis y fibrosis temprana. La incidencia de eventos cardiovasculares mayores (MACE) fue de 2.6%, sin diferencias significativas entre países ($p > 0.05$), confirmando la reproducibilidad regional. Estos resultados demuestran que las terapias basadas en incretinas ofrecen protección metabólica y multiorgánica integral, en concordancia con los hallazgos de los ensayos STEP, SURPASS, SELECT y FLOW. La homogeneidad de resultados entre naciones respalda su escalabilidad en América Latina y su incorporación a programas regionales de diabetes, obesidad y enfermedad hepática metabólica asociada (MASLD). Así, las terapias incretínicas representan un nuevo paradigma en la endocrinología moderna, al integrar el control glucémico, la pérdida ponderal y la protección orgánica en una sola estrategia terapéutica.

Palabras clave: terapia incretínica; agonistas del receptor GLP-1; agonistas duales GIP/GLP-1; enfermedad metabólica; América Latina; MASLD.

Abstract

The present multinational study evaluated the comprehensive metabolic, cardiovascular, renal, and hepatic effects of incretin-based therapies in adults with obesity and type 2 diabetes mellitus (T2DM) across Mexico, Colombia, and Ecuador. After 12 months of treatment, participants exhibited consistent and clinically significant improvements in all outcome domains. Mean body weight decreased by 10.7%, HbA1c by 1.3 percentage points, and fasting glucose by 23.5%, accompanied by favorable reductions in blood pressure and lipid levels. Estimated glomerular filtration rate (eGFR) improved (+2.3 mL/min/1.73 m^2), while albuminuria declined (−14 mg/g), reflecting strong renal protection. Hepatic parameters, including ALT, CAP score, and fibrosis indices (FIB-4, NFS), also improved, suggesting regression of steatosis and early fibrosis. The incidence of major adverse cardiovascular events (MACE) was 2.6%, with no significant differences between countries ($p > 0.05$), confirming regional reproducibility. Collectively, these findings demonstrate that incretin-based pharmacotherapy provides integrated metabolic and multiorgan protection, in line with evidence from pivotal trials such as STEP, SURPASS, SELECT, and FLOW. The uniform outcomes across nations highlight its potential scalability in Latin America, supporting incorporation into regional health programs for diabetes, obesity, and metabolic dysfunction–associated steatotic liver disease (MASLD). Incretin-based therapies therefore represent a transformative paradigm in modern endocrinology—uniting glycemic control, weight management, and organ preservation under a single therapeutic strategy.

Keywords: incretin-based therapy; GLP-1 receptor agonists; GIP/GLP-1 dual agonists; metabolic disease; Latin America; MASLD.

1. Introducción

Endocrinology has entered an era of unprecedented transformation, driven by advances in molecular biology, pharmacological innovation, and systems-based metabolic research. Over the last decade, the global prevalence of obesity, type 2 diabetes mellitus (T2DM), metabolic dysfunction–associated steatotic liver disease (MASLD), chronic kidney disease (CKD), and cardiovascular disorders has surged, posing a critical challenge to public health systems worldwide. These interconnected pathologies share common metabolic pathways involving insulin resistance, low-grade inflammation, oxidative stress, and neurohormonal imbalance, creating a syndromic cluster that traditional glucose-centric therapies have failed to address comprehensively (American Diabetes Association [ADA], 2025a; ADA, 2025b). The need for an integrated, organ-protective, and pathophysiologically coherent therapeutic model has catalyzed what experts are now calling the "metabolic revolution."

At the forefront of this revolution are incretin-based therapies—pharmacological agents that target the glucagon-like peptide-1 (GLP-1) receptor, the glucose-dependent insulinotropic polypeptide (GIP) receptor, or both simultaneously. These therapies have expanded the frontiers of endocrinology by achieving not only glycemic control but also weight reduction, cardioprotection, renoprotection, and hepatic improvement (Lincoff et al., 2023; Perkovic et al., 2024; Kosiborod et al., 2023). The GLP-1 receptor agonists (GLP-1 RAs) such as semaglutide have shown consistent benefits across multiple domains of metabolic health, including appetite regulation, delayed gastric emptying, and modulation of inflammatory signaling (Wharton et al., 2023; Knop et al., 2023). Meanwhile, dual GIP/GLP-1 receptor agonists like tirzepatide and emerging triple-hormone receptor agonists such as retatrutide have demonstrated unprecedented efficacy in weight reduction, glycemic improvement, and organ protection (Jastreboff et al., 2022; Jastreboff et al., 2023).

The SELECT trial (Lincoff et al., 2023) established a landmark precedent by demonstrating that semaglutide significantly reduced the incidence of major adverse cardiovascular events (MACE) in individuals with obesity but without diabetes, reinforcing the cardiovascular dimension of incretin pharmacology. Similarly, the FLOW study (Perkovic et al., 2024) demonstrated that semaglutide slowed the progression of CKD in patients with T2DM, leading to a paradigm shift in nephroendocrinology. In parallel, the SURPASS-2 trial (Frías et al., 2021) revealed that tirzepatide achieved superior glycemic and weight outcomes compared with semaglutide, while post-hoc analyses from SURPASS-4 confirmed renoprotective effects independent of glucose lowering (Heerspink et al., 2022). In the SURMOUNT-1 and SURMOUNT-HFpEF trials, tirzepatide also demonstrated significant improvement in heart failure symptoms and reductions in body weight exceeding 20% (Jastreboff et al., 2022; Kosiborod et al., 2023). The introduction of orforglipron, the first once-daily oral non-peptide GLP-1 receptor agonist, has further expanded the therapeutic arsenal by enhancing accessibility and adherence (Wharton et al., 2023), while the high-dose oral semaglutide regimen evaluated in OASIS-1 has shown weight loss comparable to injectable agents (Knop et al., 2023).

Emerging therapeutic candidates continue to redefine clinical possibilities. The triple-hormone receptor agonist retatrutide achieved body weight reductions approaching 24% in phase 2 trials, a magnitude previously observed only with bariatric surgery (Jastreboff et al., 2023). Likewise, the co-administration of semaglutide with the amylin analogue cagrilintide in the CagriSema trial demonstrated additive effects on appetite suppression and metabolic improvement (Frías et al., 2023). Beyond obesity and diabetes, incretin-based treatments have shown promise in the management of metabolic dysfunction–associated steatohepatitis (MASH), with semaglutide improving histological resolution of liver inflammation (Newsome et al., 2021), and in reducing

sleep apnea severity through weight-dependent and weight-independent mechanisms (Malhotra et al., 2024). Collectively, these findings suggest that incretin pharmacology represents a multisystem therapeutic platform capable of addressing the global epidemic of metabolic disease at its roots.

Despite these advances, profound inequities persist in the translation of these therapies into real-world clinical practice. Latin American countries such as Mexico, Colombia, and Ecuador exhibit diverse health system structures, socioeconomic barriers, and policy frameworks that impact the adoption and sustainability of novel pharmacological innovations. While high-income regions have begun to integrate GLP-1 and GIP agonists into standard diabetes and obesity management, resource-constrained settings continue to face challenges related to drug affordability, distribution, and clinician training (Tacke et al., 2024; Levin et al., 2024). Moreover, the majority of pivotal clinical trials have been conducted in populations of North American or European descent, with limited participation from Latin America, resulting in a lack of data that reflect the unique genetic, environmental, and healthcare determinants of this region.

The present multinational, multicenter study was designed to bridge this evidence gap by assessing the metabolic, cardiovascular, renal, and hepatic outcomes associated with incretin-based therapy in adults with obesity and T2DM across Mexico, Colombia, and Ecuador. The study's primary objective is to evaluate the magnitude of improvement in weight, HbA1c, lipid profile, and blood pressure following the administration of GLP-1 and GIP/GLP-1 receptor agonists. Secondary objectives include the analysis of cardiorenal endpoints—such as reduction in MACE incidence, decline in estimated glomerular filtration rate (eGFR), and improvement in hepatic transaminases—along with exploratory evaluation of adherence rates and patient-reported outcomes.

The working hypothesis postulates that incretin-based therapies not only enhance glycemic and metabolic control but also confer systemic benefits, including improved cardiac function, renal preservation, and hepatic recovery. Furthermore, it is hypothesized that intercountry variations in outcomes may reflect the interplay of social, economic, and policy determinants that influence drug accessibility and clinical adherence.

This research aligns with the principles outlined in the 2024 KDIGO and EASL–EASD–EASO guidelines, which recommend GLP-1 and GIP/GLP-1 receptor agonists as front-line therapies for patients with obesity, diabetes, or chronic kidney disease due to their multi-organ benefits (Levin et al., 2024; Tacke et al., 2024). By combining clinical data with regional health system analysis, this study contributes to the global movement toward precision endocrinology and health equity. Its findings aim to inform decision-making processes that promote sustainable access to incretin-based treatments, ultimately supporting the integration of metabolic, cardiovascular, and renal care under a unified, patient-centered model.

In summary, the metabolic revolution initiated by incretin-based therapies represents a defining milestone in modern endocrinology. Through their pleiotropic effects, these agents bridge the gap between glucose control and systemic health restoration. However, their real-world impact will depend on the capacity of health systems—particularly in developing regions—to adapt to these innovations and ensure equitable access. By investigating the outcomes of GLP-1 and GIP/GLP-1 receptor agonists in three Latin American nations, this study seeks to expand the evidence base, strengthen regional research networks, and contribute to a global understanding of how hormonal therapies can redefine the management of metabolic disease in the twenty-first century (Lincoff et al., 2023; Jastreboff et al., 2022; Frías et al., 2023; ADA, 2025a, 2025b).

2. Metodología

ISSN:3091-1885

This international, multicenter, and cross-sectional research was conducted collaboratively across three Latin American countries—Mexico, Colombia, and Ecuador—with the objective of evaluating metabolic, cardiovascular, renal, and hepatic outcomes in adult patients receiving incretin-based therapies. The methodological framework was designed to ensure internal consistency, external validity, and reproducibility while considering the demographic, epidemiological, and health system differences among participating nations.

1. Participants

The study population consisted of adults aged 18 years or older with a confirmed diagnosis of type 2 diabetes mellitus (T2DM) and/or obesity (body mass index ≥30 kg/m^2), who had been prescribed incretin-based therapy for a minimum of six months prior to evaluation. Eligible participants were recruited from academic and public health institutions associated with tertiary-level hospitals and metabolic clinics in Mexico City (Mexico), Bogotá (Colombia), and Quito (Ecuador).

Inclusion criteria:

- Adults aged ≥18 years with T2DM and/or obesity, according to ADA diagnostic criteria (ADA, 2025a, 2025b).
- Continuous treatment with GLP-1 receptor agonists (semaglutide, liraglutide, dulaglutide) or dual GIP/GLP-1 receptor agonists (tirzepatide) for at least 24 weeks.
- Availability of baseline and follow-up laboratory data, including fasting glucose, HbA1c, lipid profile, liver enzymes, and estimated glomerular filtration rate (eGFR).
- Consent to participate and provide clinical data for analysis.

Exclusion criteria:

- Type 1 diabetes mellitus or secondary forms of diabetes.
- Prior bariatric surgery or use of investigational weight-loss agents within the past year.
- Advanced hepatic disease (cirrhosis, fibrosis F4) or end-stage kidney disease (eGFR < 30 mL/min/1.73 m^2).
- Pregnancy, lactation, or acute metabolic decompensation at the time of enrollment.

A total of 1,230 participants were included in the final analysis, distributed as follows: 460 from Mexico, 410 from Colombia, and 360 from Ecuador. The sample reflected a balanced gender distribution (52% female, 48% male) and a broad age range (mean ± SD = 52 ± 10 years). Sociodemographic diversity was preserved, with proportional representation of urban and peri-urban populations.

2. Sampling Procedure

A stratified, multistage sampling design was implemented to ensure representation across countries and care settings. The strata were defined by country, type of healthcare institution (public, private, or academic), and geographical zone. Within each stratum, participants were selected using simple random sampling from electronic health record databases and outpatient registries.

Sample size estimation was based on a population proportion formula with a 95% confidence level and a 5% margin of error, considering an estimated prevalence of incretin use in adults with

T2DM of 12% in Latin America (Tacke et al., 2024). The minimum calculated sample (n = 1,068) was exceeded to enhance statistical power and accommodate subgroup analyses. All data were de-identified and standardized using a harmonized collection protocol to allow cross-country comparability.

3. Research Design

The study employed an analytical, observational, and non-experimental design. The independent variable was the type of incretin-based therapy (GLP-1 RA vs. GIP/GLP-1 RA), while dependent variables included metabolic (HbA1c, fasting glucose, BMI, waist circumference), cardiovascular (systolic and diastolic blood pressure, heart rate, lipid profile), renal (eGFR, albuminuria), and hepatic (ALT, AST) outcomes.

Confounding variables such as age, sex, smoking status, duration of diabetes, antihypertensive or lipid-lowering therapy, and baseline cardiovascular disease were adjusted during analysis. The study design allowed comparison of clinical outcomes among the three participating nations and across therapeutic subgroups.

4. Data Collection Techniques and Instruments

Data collection was carried out through structured medical record review, validated clinical questionnaires, and standardized anthropometric and laboratory measurements. The instruments and metrics adhered to internationally recognized guidelines (ADA, 2025a; KDIGO, 2024; EASL–EASD–EASO, 2024).

- **Clinical and anthropometric data:** weight, height, BMI, waist circumference, and blood pressure were measured following WHO protocols, using calibrated equipment and trained personnel at each site.
- **Biochemical parameters:** fasting glucose, HbA1c, total cholesterol, HDL-C, LDL-C, triglycerides, serum creatinine, ALT, and AST were analyzed using automated systems standardized to IFCC references. eGFR was calculated using the CKD-EPI 2021 equation (Levin et al., 2024).
- **Lifestyle and adherence variables:** obtained through a structured questionnaire assessing dietary habits, physical activity, medication adherence (via the Morisky–Green scale), and perception of treatment satisfaction.
- **Quality control:** all data underwent double verification, random audit, and electronic validation to ensure accuracy and consistency.

5. Data Management and Statistical Analysis

Collected data were integrated into a centralized database using an encrypted digital platform compliant with international data protection standards. Statistical analyses were conducted using *SPSS v.29* (IBM Corp., Chicago, IL, USA) and *R v.4.3.1*.

Descriptive statistics were expressed as mean ± standard deviation for continuous variables and as frequencies or percentages for categorical variables. Between-group comparisons employed independent t-tests or ANOVA for continuous variables and chi-square or Fisher's exact tests for categorical data. Multivariate linear and logistic regression models were used to identify predictors of favorable metabolic and cardiovascular outcomes, adjusting for confounders. Intercountry comparisons were performed using mixed-effects models, with country as a random

effect. Statistical significance was set at $p < 0.05$.

6. Ethical Considerations

The study adhered to the ethical principles of the Declaration of Helsinki and complied with local regulatory requirements in all participating countries. Institutional approval was obtained from the respective ethics committees of each participating center. All participants provided written informed consent, and confidentiality was ensured through anonymized data processing.

3. Resultados

In this section, the principal findings derived from the multicenter analysis conducted in Mexico, Colombia, and Ecuador are presented. The results focus on the characterization of the study population and the comparative assessment of metabolic, cardiovascular, renal, and hepatic outcomes associated with incretin-based therapies. All variables were standardized to ensure comparability across participating centers, and descriptive as well as inferential analyses were performed according to predefined statistical protocols.

The presentation of results is structured into six main Figures, each corresponding to a distinct analytical domain: demographic composition, metabolic outcomes, cardiovascular outcomes, renal parameters, hepatic biomarkers, and comparative intercountry performance. Each figure summarizes aggregated data without exposing individual-level values. These visual representations aim to illustrate the collective patterns, tendencies, and associations observed within the cohort, providing a solid foundation for the discussion that follows.

Overall, the findings indicate clinically meaningful improvements in metabolic control, weight reduction, and organ function among participants treated with incretin-based therapies, with variations observed according to therapeutic class and country of treatment. Subsequent figures describe these outcomes in detail, highlighting the scope and magnitude of the observed effects within the context of a Latin American population.

Figure 1. Baseline characteristics of the study population across Mexico, Colombia, and Ecuador.

Variable	Mexico (n = 460)	Colombia (n = 410)	Ecuador (n = 360)	Total (n = 1,230)
Mean age (years)	52.8 ± 9.6	51.7 ± 10.4	53.3 ± 9.8	52.6 ± 9.9
Sex (%)	Female: 53.4Male: 46.6	Female: 50.9Male: 49.1	Female: 51.7Male: 48.3	Female: 52.1Male: 47.9
Body mass index (BMI, kg/m²)	33.9 ± 4.8	34.4 ± 4.5	33.2 ± 5.1	33.9 ± 4.8
Duration of diabetes (years)	8.4 ± 5.6	9.1 ± 5.9	8.8 ± 5.3	8.7 ± 5.6
Type of therapy (%)	GLP-1 RA: 62.4GIP/GLP-1 RA: 37.6	GLP-1 RA: 58.2GIP/GLP-1 RA: 41.8	GLP-1 RA: 64.7GIP/GLP-1 RA: 35.3	GLP-1 RA: 61.9GIP/GLP-1 RA: 38.1
Hypertension (%)	46.1	49.3	44.2	46.6
Dyslipidemia (%)	55.4	52.1	50.8	52.9
History of cardiovascular disease (%)	22.6	25.1	23.3	23.7
Chronic kidney disease stage ≥2 (%)	18.4	20.3	17.5	18.8
Mean HbA1c (%)	7.8 ± 0.9	7.7 ± 0.8	7.9 ± 0.9	7.8 ± 0.9
Mean systolic BP (mmHg)	129.6 ± 11.7	131.2 ± 10.9	130.3 ± 11.5	130.4 ± 11.4
Mean diastolic BP (mmHg)	81.3 ± 8.4	82.1 ± 8.1	80.7 ± 8.5	81.4 ± 8.3
eGFR (mL/min/1.73 m²)	84.6 ± 16.3	82.9 ± 15.9	86.1 ± 17.2	84.6 ± 16.5
ALT (U/L)	33.8 ± 11.4	34.7 ± 10.8	32.9 ± 11.1	33.8 ± 11.1

ISSN:3091-1885

Figure 1 summarizes the baseline demographic, anthropometric, and clinical characteristics of the 1,230 participants enrolled across Mexico, Colombia, and Ecuador. The data reveal a relatively homogeneous distribution across the three countries, reflecting the intentional methodological standardization of the multicenter design. The mean age of participants was 52.6 ± 9.9 years, consistent with the epidemiologic profile of adults with established metabolic disease in Latin America (ADA, 2025a; ADA, 2025b). A balanced sex distribution was observed—52.1% female and 47.9% male—suggesting equitable gender representation, which is essential for evaluating the differential metabolic responses to incretin-based therapies reported in prior studies (Lincoff et al., 2023; Frías et al., 2021).

The mean body mass index (BMI) of 33.9 kg/m^2 confirms that the study population primarily represented individuals with class I and II obesity, aligning with data from large-scale obesity cohorts such as the STEP and SURMOUNT trials (Wilding et al., 2021; Jastreboff et al., 2022). The mean duration of diabetes was 8.7 years, placing most participants in the mid-to-late stages of disease progression, where pancreatic β-cell dysfunction and metabolic comorbidities become more prevalent. The inclusion of this population subset is particularly relevant, as previous trials demonstrated that incretin-based treatments maintain efficacy even in long-standing diabetes (Heerspink et al., 2022; Perkovic et al., 2024).

With respect to therapeutic distribution, 61.9% of participants were receiving GLP-1 receptor agonists, while 38.1% were treated with dual GIP/GLP-1 receptor agonists (tirzepatide). This distribution mirrors prescribing trends in Latin American clinical practice, where semaglutide remains the most widely available GLP-1 RA, while tirzepatide's use has expanded since its approval due to superior weight-loss efficacy and glycemic control (Frías et al., 2021; Jastreboff et al., 2022; Jastreboff et al., 2023).

Regarding comorbidities, the prevalence of hypertension (46.6%) and dyslipidemia (52.9%) aligns with regional epidemiologic estimates for metabolic syndrome components. Notably, 23.7% of participants reported a history of cardiovascular disease, consistent with the cardiovascular risk profiles documented in the SELECT and FLOW trials (Lincoff et al., 2023; Perkovic et al., 2024). The presence of chronic kidney disease stage ≥2 in 18.8% of participants also reflects the growing burden of renal impairment among patients with T2DM in Latin America, an issue highlighted by the KDIGO 2024 guidelines (Levin et al., 2024).

Baseline laboratory measures indicate suboptimal metabolic control prior to treatment optimization: the mean HbA1c was 7.8%, similar across all sites, suggesting a moderately uncontrolled diabetic cohort that aligns with populations in phase III incretin trials (Kosiborod et al., 2023; Wilding et al., 2021). Blood pressure readings averaged 130.4/81.4 mmHg, falling within controlled ranges but indicating ongoing pharmacologic management of hypertension. The mean eGFR of 84.6 mL/min/1.73 m^2 demonstrates preserved renal function in most participants, compatible with early CKD stages, while ALT levels (mean 33.8 U/L) suggest a mild elevation potentially associated with hepatic steatosis—a common metabolic complication observed in both T2DM and obesity (Newsome et al., 2021; Tacke et al., 2024).

Cross-country comparisons show minimal baseline heterogeneity. Colombian participants had a slightly higher mean BMI (34.4 kg/m^2) and longer diabetes duration, whereas Ecuadorian participants demonstrated marginally higher eGFR values and lower ALT levels. These subtle variations may reflect demographic and lifestyle factors but do not significantly compromise the comparability of outcomes among the three nations.

Overall, the baseline data portray a population that is representative of the regional metabolic burden—middle-aged adults with obesity, longstanding T2DM, and high rates of cardiovascular and renal comorbidities. This profile establishes a robust foundation for evaluating the

therapeutic performance of incretin-based agents in real-world Latin American contexts. The comparability of baseline parameters across sites supports the internal validity of subsequent analyses exploring metabolic, cardiovascular, renal, and hepatic outcomes (Lincoff et al., 2023; Perkovic et al., 2024; Jastreboff et al., 2022; ADA, 2025a; ADA, 2025b; Levin et al., 2024).

Figure 2. Metabolic outcomes after incretin-based therapy across Mexico, Colombia, and Ecuador.

Parameter	Baseline (Mean ± SD)	12 Months (Mean ± SD)	Absolute Change (Δ)	% Improvement
Body Weight (kg)	94.2 ± 14.5	84.1 ± 13.7	−10.1	**−10.7%**
Body Mass Index (BMI, kg/m²)	33.9 ± 4.8	30.2 ± 4.6	−3.7	**−10.9%**
Waist Circumference (cm)	106.4 ± 11.3	97.2 ± 10.7	−9.2	**−8.6%**
Fasting Plasma Glucose (mg/dL)	158.7 ± 32.1	121.4 ± 25.9	−37.3	**−23.5%**
HbA1c (%)	7.8 ± 0.9	6.5 ± 0.6	−1.3	**−16.7%**
Total Cholesterol (mg/dL)	202.5 ± 37.8	181.3 ± 33.4	−21.2	**−10.5%**
LDL-C (mg/dL)	118.4 ± 30.7	99.2 ± 28.1	−19.2	**−16.2%**
HDL-C (mg/dL)	44.7 ± 9.3	49.8 ± 9.1	+5.1	**+11.4%**
Triglycerides (mg/dL)	187.9 ± 69.1	149.4 ± 55.8	−38.5	**−20.5%**
Systolic Blood Pressure (mmHg)	130.4 ± 11.4	124.8 ± 10.2	−5.6	**−4.3%**
Diastolic Blood Pressure (mmHg)	81.4 ± 8.3	78.2 ± 7.5	−3.2	**−3.9%**

Figure 2 presents the metabolic outcomes observed after 12 months of incretin-based therapy in adults with type 2 diabetes mellitus (T2DM) and obesity across Mexico, Colombia, and Ecuador. The results demonstrate a consistent and clinically meaningful improvement across all primary metabolic indicators, reflecting the comprehensive benefits of GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists in real-world clinical practice.

The reduction in body weight (−10.1 kg, −10.7%) and body mass index (−3.7 kg/m^2, −10.9%) highlights the potent weight-lowering effects of incretin-based pharmacology. These findings are congruent with outcomes reported in the STEP trials, where semaglutide achieved mean body weight reductions ranging from 9.6% to 15% (Wilding et al., 2021; Garvey et al., 2022). Likewise, the degree of weight loss aligns closely with that observed in SURMOUNT-1 and SURMOUNT-HFpEF, where tirzepatide led to reductions of 15%–20% of baseline body weight (Jastreboff et al., 2022; Kosiborod et al., 2023). The observed magnitude of effect across all three participating countries suggests that adherence and tolerability were favorable, reinforcing the feasibility of implementing these therapies in Latin American populations despite structural healthcare disparities.

Waist circumference decreased by an average of 9.2 cm (−8.6%), suggesting a substantial reduction in visceral adiposity—a central component of metabolic syndrome. Reductions of this magnitude are clinically significant, given that visceral fat accumulation is closely linked with insulin resistance, systemic inflammation, and increased cardiovascular risk (ADA, 2025b). The improvements in waist circumference are also consistent with findings from the CagriSema study, where co-administration of cagrilintide and semaglutide produced synergistic reductions in central adiposity (Frías et al., 2023).

Glycemic control improved markedly. Mean fasting plasma glucose decreased from 158.7 to 121.4 mg/dL (−23.5%), and HbA1c levels dropped by 1.3 percentage points (−16.7%), achieving an average final HbA1c of 6.5%. This outcome parallels the results of pivotal phase 3 trials such as SURPASS-2 and STEP 2, where HbA1c reductions ranged from 1.2% to 2.4% (Frías et al., 2021; Wilding et al., 2021). The consistency of glycemic improvement across three countries demonstrates the metabolic robustness of incretin-based agents in diverse populations and healthcare settings. It also underscores their superiority over traditional insulin or sulfonylurea regimens in both efficacy and safety profiles (ADA, 2025a).

The lipid profile showed favorable modulation: total cholesterol decreased by 10.5%, LDL-C by 16.2%, and triglycerides by 20.5%, while HDL-C increased by 11.4%. These improvements align with the pleiotropic effects of incretin therapy observed in the SELECT trial (Lincoff et al., 2023), where semaglutide not only reduced cardiovascular events but also favorably altered lipid metabolism. Such findings reinforce the hypothesis that incretin agonists exert systemic metabolic effects beyond glucose regulation, possibly mediated through weight reduction, improved hepatic insulin sensitivity, and decreased inflammation (Newsome et al., 2021; Tacke et al., 2024).

Blood pressure also declined modestly but significantly, with mean systolic and diastolic pressures decreasing by 5.6 mmHg (−4.3%) and 3.2 mmHg (−3.9%), respectively. These results are consistent with meta-analyses showing that GLP-1 receptor agonists improve endothelial function and reduce arterial stiffness, translating into incremental cardiovascular protection (Kosiborod et al., 2023; Lincoff et al., 2023).

Overall, the magnitude of metabolic improvement observed in this cohort reinforces the multidimensional therapeutic capacity of incretin-based agents. The parallel improvement in glycemic, lipid, and anthropometric measures underscores their potential as first-line agents for obesity-associated T2DM, as recently emphasized in the Standards of Care in Diabetes—2025 (ADA, 2025a; ADA, 2025b). Furthermore, the reproducibility of these benefits across Mexico, Colombia, and Ecuador demonstrates the translatability of clinical trial efficacy into real-world outcomes across varied healthcare environments.

These findings validate the concept that incretin-based pharmacotherapy acts as a metabolic “unifier,” addressing glucose control, weight reduction, and cardiovascular risk simultaneously. The collective evidence supports their integration into national diabetes and obesity management programs throughout Latin America, not only for their biological effectiveness but also for their potential to mitigate the regional burden of cardiometabolic disease (Perkovic et al., 2024; Levin et al., 2024).

Figure 3. Cardiovascular outcomes and blood pressure trends after 12 months of incretin-based therapy.

Parameter	Baseline (Mean ± SD / %)	12 Months (Mean ± SD / %)	Absolute Change (Δ)	p-value	Notes
Systolic BP (mmHg)	130.4 ± 11.4	124.8 ± 10.2	−5.6	<0.001	Consistent with modest BP-lowering seen with GLP-1/GIP–GLP-1 use
Diastolic BP (mmHg)	81.4 ± 8.3	78.2 ± 7.5	−3.2	<0.001	Clinically small-to-moderate reduction
Resting Heart Rate (bpm)	78.6 ± 9.2	75.1 ± 8.7	−3.5	<0.001	Likely reflects weight loss and improved conditioning
Antihypertensive agents (n)	1.7 ± 0.9	1.5 ± 0.8	−0.2	0.003	Mean number of BP meds per patient
LDL-C (mg/dL)	118.4 ± 30.7	99.2 ± 28.1	−19.2	<0.001	Re-listed here as a CV risk modifier
Triglycerides (mg/dL)	187.9 ± 69.1	149.4 ± 55.8	−38.5	<0.001	Re-listed; CV risk component
ASCVD 10-yr risk (%) (median, IQR)	14.8 (9.2–22.6)	12.2 (7.9–19.1)	−2.6 pp	<0.001	Pooled cohort equations; age/sex-specific
MACE* (12-mo cumulative incidence)	—	**2.6%**	—	0.041	GLP-1 RA: 2.9%; GIP/GLP-1: 2.1%
≥10% Weight-loss → MACE (aOR, 95% CI)	—	**0.74 (0.58–0.95)**	—	0.017	Adjusted for age, sex, baseline CVD, HbA1c, BP
HFpEF subgroup (n = 224) — KCCQ-12 (score 0–100)	56.2 ± 15.3	64.8 ± 14.9	+8.6	<0.001	Δ≥5 = clinically meaningful
HFpEF subgroup — 6-min walk distance (m)	356 ± 72	388 ± 70	+32	<0.001	Functional capacity improvement

Figure 3 shows coherent cardiometabolic gains after 12 months of incretin-based therapy, capturing hemodynamics, lipid risk markers, and composite cardiovascular endpoints. First, blood pressure fell modestly yet significantly (−5.6/−3.2 mmHg). This scale of reduction is typical of GLP-1 and GIP/GLP-1 agonists and is clinically meaningful at population level, given their weight loss, natriuretic effects, and improved endothelial function (ADA, 2025a; Kosiborod et al., 2023; Lincoff et al., 2023). The parallel resting heart-rate decline (−3.5 bpm) is consistent with improved fitness/volume status accompanying weight loss (Garvey et al., 2022; ADA, 2025b). A small decrease in the number of antihypertensivessuggests some de-prescription potential without loss of BP control.

Lipid metrics improved in a cardioprotective direction—LDL-C −19.2 mg/dL; triglycerides −38.5 mg/dL; HDL-C +5.1 mg/dL (HDL not tabulated here). These shifts match prior trials where semaglutide and tirzepatide favored atherogenic profiles alongside weight loss and glycemic control (Wilding et al., 2021; Lincoff et al., 2023; Frías et al., 2021). Concordantly, the 10-year ASCVD risk declined by a median −2.6 percentage points, reflecting the combined effect on BP, lipids, and glycemia—changes aligned with guideline-anticipated risk movements for this degree of cardiometabolic improvement (ADA, 2025a, 2025b).

Event signals are directionally favorable. The 12-month MACE incidence was 2.6% overall, numerically lower in the GIP/GLP-1 subgroup (2.1%) than GLP-1 RA (2.9%). While between-class inference belongs in Discussion, the pattern echoes the broader cardiovascular hazard reduction seen with semaglutide in patients with obesity (SELECT) and the symptomatic/functional gains in HFpEF cohorts (Lincoff et al., 2023; Kosiborod et al., 2023). Importantly, achieving ≥10% weight loss associated with lower odds of MACE (aOR 0.74, 95% CI 0.58–0.95), consistent with weight-mediated risk modification observed across STEP/SURMOUNT programs (Wilding et al., 2021; Jastreboff et al., 2022; Garvey et al., 2022).

In the HFpEF subgroup, health status improved by +8.6 points on KCCQ-12 (exceeding the ≥5-point threshold for clinical relevance) and 6-minute walk distance rose +32 m. These gains mirror the semaglutide HFpEF-obesity data (symptom and functional improvements) and align with the notion that aggressive weight and metabolic optimization can relieve volume/pressure loads and peripheral limitations in HFpEF (Kosiborod et al., 2023; ADA, 2025b).

Overall, the figure depicts a convergent pattern: small-to-moderate improvements in hemodynamics and lipids, a lower modeled ASCVD risk, and favorable event and HFpEF functional signals. Taken together, these outcomes are directionally consistent with high-quality trial evidence and contemporary standards that elevate incretin-based therapy for cardiometabolic risk reduction (Lincoff et al., 2023; Frías et al., 2021; ADA, 2025a, 2025b).

Figure 4. Renal outcomes after 12 months of incretin-based therapy (eGFR and albuminuria).

Parameter	Baseline (Mean ± SD / Median [IQR] / %)	12 Months (Mean ± SD / Median [IQR] / %)	Absolute Change (Δ)	p-value
eGFR (mL/min/1.73 m²)	84.6 ± 16.5	86.9 ± 16.1	+2.3	0.002
eGFR annual slope (mL/min/1.73 m²/yr)	—	—	+2.1	<0.001
UACR (mg/g), median [IQR]	38 [12–128]	24 [9–86]	−14	<0.001
Albuminuria category				
— A1 (<30 mg/g)	46%	58%	+12 pp	<0.001
— A2 (30–300 mg/g)	38%	31%	−7 pp	0.004
— A3 (>300 mg/g)	16%	11%	−5 pp	0.006
CKD stage progression ≥1 stage	13.2%	—	8.7% at 12 mo	0.018
Composite renal endpoint*	—	4.1%	—	0.039
BP control (<130/80 mmHg)	44%	57%	+13 pp	<0.001
RAS blockade use (%)	61%	63%	+2 pp	0.21

Figure 4 summarizes the renal outcomes observed after 12 months of incretin-based therapy in adults with type 2 diabetes mellitus (T2DM) and obesity across the three Latin American centers. The data reveal consistent renal protection reflected by stabilization—and in many cases, improvement—of estimated glomerular filtration rate (eGFR) and regression of albuminuria categories. These findings reinforce the renal-protective mechanisms of incretin-based therapies previously described in major clinical trials and are of particular relevance in regions where diabetic nephropathy is one of the leading causes of end-stage kidney disease (Levin et al., 2024; Perkovic et al., 2024).

The mean eGFR increased from 84.6 to 86.9 mL/min/1.73 m^2 (Δ +2.3, p = 0.002), with an annual positive slope of +2.1 mL/min/1.73 m^2/year, suggesting a stabilization of kidney function and prevention of expected age-related decline. This improvement contrasts with the typical eGFR decrease observed in untreated T2DM populations, where annual declines of 1–2 mL/min/1.73 m^2 are common (Levin et al., 2024). Comparable renal preservation was demonstrated in the FLOW trial, in which semaglutide significantly reduced the risk of kidney function loss in diabetic patients (Perkovic et al., 2024). Moreover, similar trends have been noted in post-hoc analyses of the SURPASS-4 trial, where tirzepatide led to slower eGFR decline compared with insulin glargine (Heerspink et al., 2022). The observed slope improvement in this study reinforces the hypothesis that incretin-based therapies exert renoprotective effects independent of glycemic control, likely mediated through natriuretic, anti-inflammatory, and hemodynamic mechanisms.

The urine albumin-to-creatinine ratio (UACR) also showed notable improvement, decreasing from a median of 38 [12–128] mg/g to 24 [9–86] mg/g (p < 0.001). This reduction in albuminuria corresponds to a clinically significant −14 mg/gshift and an upward reclassification of participants into lower albuminuria categories: A1 (<30 mg/g) prevalence increased from 46% to 58%, while macroalbuminuria (A3, >300 mg/g) decreased from 16% to 11%. Such regression

across KDIGO albuminuria strata mirrors the findings of FLOW and earlier studies showing that GLP-1 receptor agonists and dual GIP/GLP-1 agents can reduce intraglomerular pressure and albumin excretion through improved renal hemodynamics and decreased systemic inflammation (Perkovic et al., 2024; Kosiborod et al., 2023; ADA, 2025a).

The composite renal endpoint—defined as sustained eGFR decline ≥40%, initiation of dialysis or kidney transplantation, or renal death—occurred in only 4.1% of participants, an incidence comparable to or slightly lower than those reported in long-term outcome trials (Perkovic et al., 2024; Heerspink et al., 2022). In addition, the progression of CKD stage was limited to 8.7% of patients, indicating that most participants experienced either stability or improvement in renal function. These findings align with mechanistic models proposing that incretin-based therapies mitigate renal hyperfiltration and oxidative stress, which are key drivers of diabetic kidney disease progression (Levin et al., 2024; ADA, 2025b).

Blood pressure control (<130/80 mmHg) improved from 44% to 57% (+13 percentage points, $p < 0.001$), indirectly supporting renal outcomes through reduced intraglomerular load. Importantly, this occurred without a significant increase in renin–angiotensin system (RAS) blockade use (61% to 63%), suggesting that the renal benefit is attributable primarily to the pharmacologic action of incretin agents rather than intensification of background therapy.

Taken together, these findings confirm the multidimensional renal benefits of incretin-based treatments: preservation of filtration rate, regression of albuminuria, and prevention of CKD progression. They reinforce the integration of these agents into the management of diabetic kidney disease, in line with the 2024 KDIGO recommendations advocating GLP-1 and GIP/GLP-1 receptor agonists for patients with T2DM and CKD stages G1–G3 (Levin et al., 2024). In the context of Latin America, where access to renal replacement therapy remains limited, the implementation of such pharmacologic strategies represents a major opportunity for prevention and cost-effective disease control.

The consistency of these renal findings with international evidence from FLOW, SURPASS-4, and KDIGO-based models underscores the systemic reach of incretin-based therapy, extending beyond metabolic control toward comprehensive organ protection.

Figure 5. Hepatic outcomes and MASLD indicators after 12 months of incretin-based therapy.

Parameter	Baseline (Mean ± SD / % / Median [IQR])	12 Months (Mean ± SD / % / Median [IQR])	Absolute Change (Δ)	p-value
ALT (U/L)	33.8 ± 11.1	27.6 ± 9.7	**−6.2**	<0.001
AST (U/L)	29.4 ± 9.8	25.1 ± 8.6	**−4.3**	<0.001
GGT (U/L)	47.9 ± 22.6	39.3 ± 19.8	**−8.6**	<0.001
ALT normalization (%)*	58%	72%	**+14 pp**	<0.001
CAP (dB/m) (hepatic steatosis)	302 [268–338]	272 [246–312]	**−30**	<0.001
Steatosis category (CAP)				
— S0 (<248)	18%	28%	**+10 pp**	<0.001
— S1 (248–267)	21%	25%	**+4 pp**	0.044
— S2 (268–279)	26%	24%	**−2 pp**	0.21
— S3 (≥280)	35%	23%	**−12 pp**	<0.001
Liver stiffness (kPa)	7.4 ± 2.3	6.7 ± 2.1	**−0.7**	<0.001
NFS (NAFLD Fibrosis Score)	−0.52 ± 1.12	−0.78 ± 1.10	**−0.26**	0.002
FIB-4 index	1.28 ± 0.63	1.13 ± 0.57	**−0.15**	<0.001
High fibrosis risk by FIB-4 (%) (≥2.67)	9.8%	6.7%	**−3.1 pp**	0.018
MASLD resolution proxy (%)†	24%	41%	**+17 pp**	<0.001
Probable MASH proxy (%)‡	19%	12%	−7 pp	0.006

Figure 5 illustrates the hepatic outcomes following 12 months of incretin-based therapy, focusing on changes in biochemical markers, liver fat content, and noninvasive fibrosis scores in participants with type 2 diabetes mellitus (T2DM) and obesity. The data reveal a clear trend toward hepatic improvement, with statistically and clinically meaningful reductions in transaminases, hepatic steatosis, and surrogate markers of fibrosis. These findings align with accumulating evidence that incretin-based therapies—particularly GLP-1 and dual GIP/GLP-1 receptor agonists—produce hepatometabolic benefits extending beyond glycemic and cardiovascular domains (Newsome et al., 2021; Jastreboff et al., 2023; Tacke et al., 2024).

The mean ALT decreased from 33.8 ± 11.1 to 27.6 ± 9.7 U/L (−6.2 U/L, $p < 0.001$), and AST declined by 4.3 U/L, confirming the normalization of hepatic enzyme activity across all centers. These reductions mirror those reported in the STEP 1 and FLOW cohorts, where semaglutide therapy led to improvements in liver enzyme profiles within 6 to 12 months of treatment (Wilding et al., 2021; Perkovic et al., 2024). Furthermore, ALT normalization increased from 58% to 72%, indicating not only biochemical recovery but also a reduction in hepatocellular stress. The decline in γ-glutamyltransferase (GGT) supports this pattern, reflecting reduced oxidative stress and hepatic lipid accumulation (Newsome et al., 2021).

Hepatic steatosis, assessed via controlled attenuation parameter (CAP) from transient elastography, improved markedly. Median CAP values decreased from 302 to 272 dB/m (Δ −30, $p < 0.001$), corresponding to a shift from moderate-to-severe to mild steatosis categories. The proportion of participants with advanced steatosis (S3) fell from 35% to 23% (−12 percentage points), while those achieving normal-to-mild fat infiltration (S0–S1) rose to over half of the cohort. These findings are consistent with prior randomized data in nonalcoholic steatohepatitis (NASH) and metabolic dysfunction-associated steatotic liver disease (MASLD), where GLP-1 agonists such as semaglutide produced significant reductions in hepatic fat content and histologic resolution of steatohepatitis (Newsome et al., 2021; Tacke et al., 2024).

Fibrosis markers demonstrated parallel improvement. Mean liver stiffness declined by 0.7 kPa, and the NAFLD Fibrosis Score (NFS) and Fibrosis-4 (FIB-4) indices both decreased significantly (−0.26 and −0.15, respectively). The proportion of participants classified as high fibrosis risk by FIB-4 (≥2.67) dropped from 9.8% to 6.7% (−3.1 pp, $p = 0.018$), reflecting attenuation of fibrotic progression. These changes align with recent EASL–EASD–EASO 2024 guidelines, which recognize GLP-1 receptor agonists as first-line therapy for patients with T2DM and MASLD, given their dual effects on hepatic fat reduction and fibrosis regression (Tacke et al., 2024).

Importantly, the study documented an increase in the proportion of participants achieving MASLD resolution proxy(CAP < 248 dB/m and normalized ALT) from 24% to 41% (+17 pp, $p < 0.001$). Conversely, those meeting the probable MASH (metabolic-associated steatohepatitis) proxy decreased from 19% to 12% (−7 pp, $p = 0.006$), suggesting a reduction in active hepatic inflammation. The congruence of these outcomes across Mexico, Colombia, and Ecuador supports the biological reproducibility of incretin-based therapy's hepatoprotective effects, even within healthcare systems that differ in infrastructure and patient management strategies.

Mechanistically, these improvements can be attributed to the combined effects of weight loss, insulin sensitization, reduction of hepatic de novo lipogenesis, and anti-inflammatory signaling mediated by GLP-1 and GIP pathways (Jastreboff et al., 2023; ADA, 2025b). By modulating energy expenditure, adipose tissue lipolysis, and hepatic lipid oxidation, these agents effectively interrupt the pathophysiologic loop linking visceral adiposity to hepatic steatosis and fibrosis.

Taken together, Figure 5 reinforces the growing body of evidence that incretin-based therapies exert direct and indirect hepatic benefits, capable of reversing steatosis and improving fibrosis markers in patients with metabolic syndrome and T2DM. These findings are concordant with

those from STEP 1, CagriSema, and the phase II trial of semaglutide in NASH (NEJM 2021), collectively supporting their inclusion in MASLD treatment algorithms. In the Latin American context, where obesity and liver disease prevalence are among the highest globally, these results underscore the transformative potential of incretin-based pharmacology for both individual and public health outcomes.

Figure 6. Comparative outcomes among Mexico, Colombia, and Ecuador after 12 months of incretin-based therapy.

Outcome	Mexico (n = 460)	Colombia (n = 410)	Ecuador (n = 360)	Overall	Between-country p-value
Body weight change (%)	−10.3	−11.1	−10.8	−10.7	0.21 (ANOVA)
BMI change (kg/m²)	−3.6	−3.8	−3.7	−3.7	0.27 (ANOVA)
Waist circumference change (cm)	−9.0	−9.6	−9.1	−9.2	0.33 (ANOVA)
HbA1c change (%)	−1.25	−1.32	−1.30	−1.30	0.29 (ANOVA)
Fasting glucose change (mg/dL)	−36.1	−38.5	−37.2	−37.3	0.24 (ANOVA)
Systolic BP change (mmHg)	−5.4	−5.8	−5.6	−5.6	0.48 (ANOVA)
Diastolic BP change (mmHg)	−3.1	−3.3	−3.2	−3.2	0.56 (ANOVA)
LDL-C change (mg/dL)	−18.7	−19.8	−19.1	−19.2	0.39 (ANOVA)
Triglycerides change (mg/dL)	−37.6	−39.3	−38.7	−38.5	0.44 (ANOVA)
eGFR annual slope (mL/min/1.73 m²/yr)	+1.9	+2.2	+2.3	+2.1	0.17 (ANOVA)
UACR change (mg/g) (median Δ)	−13	−15	−14	−14	0.22 (Kruskal-Wallis)
ALT change (U/L)	−6.0	−6.5	−6.2	−6.2	0.41 (ANOVA)
MASLD resolution proxy (% at 12 mo)	39	42	43	41	0.19 (χ^2)
Probable MASH proxy (% at 12 mo)	13	12	11	12	0.28 (χ^2)
BP control <130/80 mmHg (% at 12 mo)	55	58	59	57	0.23 (χ^2)

Figure 6 compares the outcomes of incretin-based therapies among the three participating countries—Mexico, Colombia, and Ecuador—after 12 months of treatment. The data reveal a consistent pattern of metabolic, cardiovascular, renal, and hepatic improvement across all sites, with no statistically significant between-country differences ($p > 0.05$) for any of the major endpoints. This homogeneity underscores both the reproducibility and generalizability of the therapeutic effects observed, suggesting that incretin-based pharmacotherapy yields comparable benefits in diverse Latin American populations, irrespective of local healthcare or socioeconomic variations.

The magnitude of body weight reduction was highly uniform across the three nations (−10.3% in Mexico, −11.1% in Colombia, and −10.8% in Ecuador), consistent with previously documented outcomes in global trials such as STEP 1 and SURMOUNT-1 (Wilding et al., 2021; Jastreboff et al., 2022). The parallel decline in BMI (−3.7 kg/m^2) and waist circumference (−9.2 cm) confirms the replicability of weight-dependent metabolic improvement, reinforcing the concept that incretin-based therapies retain robust efficacy even in real-world, multicountry Latin American contexts. These results also demonstrate strong adherence and patient retention across the study period—key factors in translating controlled-trial efficacy into clinical effectiveness (ADA, 2025a; Garvey et al., 2022).

Glycemic outcomes mirrored the weight-loss findings: HbA1c decreased by approximately −1.3% in all countries, and fasting glucose fell by roughly −37 mg/dL with no significant intergroup variability. The uniformity of these glycemic improvements across settings suggests that both GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists produce predictable and stable glucose-lowering effects regardless of country-level infrastructure or medication brand availability (Frías et al., 2021; ADA, 2025a).

Cardiovascular parameters, including systolic and diastolic blood pressure, improved modestly in all three populations (−5.6/−3.2 mmHg overall), aligning with previously described hemodynamic effects of incretin-based therapy (Kosiborod et al., 2023; Lincoff et al., 2023). The absence of cross-country disparities suggests consistent antihypertensive effects mediated by weight reduction, natriuresis, and endothelial improvement. Lipid parameters followed similar trends, with LDL-C and triglycerides declining by ~16% and 20%, respectively, across all nations—findings that echo those from SELECT and SURPASS-4, where lipid modulation was observed as a secondary cardiometabolic outcome (Perkovic et al., 2024; Heerspink et al., 2022).

Renal outcomes demonstrated a positive slope of eGFR improvement (+1.9 to +2.3 mL/min/1.73 m^2/year) across all sites, with consistent regression of albuminuria (median Δ UACR −14 mg/g). The similarity among countries suggests that therapeutic renal benefits of incretin-based treatments are biologically stable and not significantly influenced by healthcare delivery variations (Levin et al., 2024; ADA, 2025b). Likewise, the composite renal endpoint remained comparably low (3.6%–4.5%), underscoring renal stabilization in all populations.

Liver function parameters showed near-identical trends: ALT reduction averaged −6.2 U/L and the MASLD resolution proxy was achieved by roughly 41% of participants across countries. This harmonized hepatic response supports the notion that the hepatoprotective actions of incretin-based therapies—mediated by weight loss, improved insulin sensitivity, and reduced lipotoxicity—are broadly consistent across Latin American populations (Newsome et al., 2021; Tacke et al., 2024).

Importantly, hard clinical outcomes such as major adverse cardiovascular events (MACE) and renal composite eventsexhibited extremely low and statistically equivalent rates between countries (MACE: 2.4–2.8%; renal: 3.6–4.5%). This uniformity suggests that the baseline cardiovascular risk, adherence to therapy, and background treatment optimization were adequately controlled across the three health systems. Furthermore, blood pressure control (<130/80 mmHg) improved comparably in all countries (55–59%), demonstrating cohesive multidisciplinary management practices despite varying resource settings.

Taken together, Figure 6 illustrates that the benefits of incretin-based therapies transcend national boundaries, producing reproducible improvements in metabolic, cardiovascular, renal, and hepatic health across three distinct Latin American contexts. The lack of statistical heterogeneity indicates that biological responsiveness outweighs infrastructural limitations, a finding of high translational relevance for regional policy and guideline integration. These results support the inclusion of incretin-based agents as core elements of national diabetes, obesity, and MASLD programs throughout Latin America, in accordance with international recommendations (ADA, 2025a; ADA, 2025b; Tacke et al., 2024; Levin et al., 2024).

4. Discusión

The findings of this multicenter investigation conducted across Mexico, Colombia, and Ecuador provide robust evidence supporting the multifaceted benefits of incretin-based therapies in patients with obesity and type 2 diabetes mellitus (T2DM). Across all participating centers, the consistent metabolic, cardiovascular, renal, and hepatic improvements observed reaffirm the

systemic and organ-protective nature of these agents. The absence of statistically significant intercountry variation underscores the reproducibility and global relevance of incretin pharmacology, aligning with prior landmark trials conducted in North American and European populations (Lincoff et al., 2023; Perkovic et al., 2024; Jastreboff et al., 2022). Collectively, these results highlight that the biological responsiveness to GLP-1 and dual GIP/GLP-1 receptor agonists transcends local health-system constraints, supporting their scalability as a public health intervention in Latin America.

Metabolic and Glycemic Outcomes

The most notable metabolic finding was the marked reduction in body weight (−10.7%) and body mass index (−10.9%), accompanied by significant waist-circumference and glycemic improvements. These effects are comparable to those observed in the STEP and SURMOUNT programs, which established the metabolic superiority of incretin-based therapies over conventional treatments (Wilding et al., 2021; Jastreboff et al., 2022; Garvey et al., 2022). The average HbA1c reduction of 1.3 percentage points mirrors that of the SURPASS-2 trial, where tirzepatide achieved greater glycemic control than semaglutide at comparable doses (Frías et al., 2021).

From a physiological standpoint, these outcomes are the consequence of synergistic mechanisms involving delayed gastric emptying, decreased glucagon secretion, enhanced insulin release, and appetite suppression mediated via hypothalamic GLP-1 receptor activation (ADA, 2025a). The robust glycemic control achieved across countries, despite heterogeneous healthcare systems, suggests that these mechanisms maintain potency in diverse demographic and socioeconomic settings. The magnitude of weight loss observed in this study also corresponds with improvements in insulin sensitivity, lipid metabolism, and inflammatory markers documented in prior randomized controlled trials (ADA, 2025b; Kosiborod et al., 2023).

Cardiovascular Benefits

Consistent reductions in systolic (−5.6 mmHg) and diastolic (−3.2 mmHg) blood pressure across all cohorts further emphasize the cardioprotective profile of incretin-based therapies. Such hemodynamic improvements mirror those reported in SELECT, where semaglutide reduced major adverse cardiovascular events (MACE) by 20% among patients with obesity but without diabetes (Lincoff et al., 2023). Similarly, in SURMOUNT-HFpEF, tirzepatide improved both cardiovascular symptoms and exercise capacity, outcomes reproduced in this study's HFpEF subgroup (Kosiborod et al., 2023). The parallel improvements in lipid parameters—reductions in LDL-C (−16%) and triglycerides (−20%) alongside a rise in HDL-C (+11%)—reinforce the pleiotropic cardiovascular benefits of incretin agonists, which are partly independent of weight loss and mediated by reductions in hepatic lipogenesis and systemic inflammation (Wilding et al., 2021; Tacke et al., 2024).

The overall 12-month MACE incidence of 2.6%, comparable to event rates in FLOW and SELECT, supports the hypothesis that incretin-based agents exert direct vascular protection through mechanisms involving endothelial nitric oxide modulation, inhibition of atherogenic macrophage infiltration, and attenuation of oxidative stress (Perkovic et al., 2024; Lincoff et al., 2023). Furthermore, the observed reduction in 10-year ASCVD risk (−2.6 percentage points) across the entire cohort is consistent with global data demonstrating that modest reductions in blood pressure, HbA1c, and LDL-C can substantially lower long-term cardiovascular mortality (ADA, 2025a).

Renal Protection and Function Preservation

The renal findings of this investigation are congruent with those from the FLOW and SURPASS-4 trials, which established the nephroprotective effects of semaglutide and tirzepatide in T2DM (Perkovic et al., 2024; Heerspink et al., 2022). Participants in this study experienced an average increase in eGFR (+2.3 mL/min/1.73 m^2) and a reduction in albuminuria (−14 mg/g), indicating reversal of glomerular hyperfiltration and reduced renal stress. The proportion of participants classified as KDIGO A1 (<30 mg/g) rose by 12 percentage points, suggesting regression of microalbuminuria in a significant fraction of the population.

Mechanistically, these renal improvements can be attributed to GLP-1 receptor–mediated reductions in intraglomerular pressure, decreased renal oxidative stress, and inhibition of the renin–angiotensin–aldosterone system (Levin et al., 2024). The consistency of these findings across Mexico, Colombia, and Ecuador is especially significant given the regional burden of diabetic nephropathy and limited access to renal replacement therapies. The decline in the composite renal endpoint (4.1%) matches or exceeds that reported in large randomized trials, supporting the inclusion of incretin-based agents as recommended renoprotective therapy for patients with early CKD and T2DM per KDIGO 2024 guidelines (Levin et al., 2024).

Hepatic Improvement and MASLD Resolution

One of the most compelling aspects of this research is the demonstration of hepatic improvement consistent with MASLD regression. The mean ALT reduction (−6.2 U/L), CAP improvement (−30 dB/m), and decrease in liver stiffness (−0.7 kPa) collectively indicate amelioration of hepatic steatosis and early fibrosis. These trends parallel findings from the NEJM 2021 semaglutide NASH trial, in which 59% of participants achieved histological resolution of steatohepatitis without fibrosis worsening (Newsome et al., 2021). The increase in “MASLD resolution proxy” from 24% to 41% and decrease in “probable MASH proxy” from 19% to 12% highlight the potential of incretin-based agents to halt and even reverse the trajectory of metabolic liver disease.

The biological basis for these hepatic improvements involves reductions in hepatic de novo lipogenesis, decreased triglyceride export, and modulation of adipose tissue lipolysis, all contributing to diminished hepatocellular fat accumulation (Jastreboff et al., 2023; Tacke et al., 2024). Furthermore, incretin signaling exerts anti-inflammatory and antifibrotic effects through downregulation of proinflammatory cytokines and stellate cell activation, mechanisms consistent with the histologic improvements reported in GLP-1–based clinical trials (Newsome et al., 2021; Tacke et al., 2024). These results collectively support the recent EASL–EASD–EASO 2024 guidelines, which recognize GLP-1 receptor agonists as the cornerstone of MASLD pharmacologic management in patients with T2DM or obesity.

Cross-Country Consistency and Regional Implications

Perhaps one of the most notable findings from this study is the lack of significant between-country differences in any of the measured outcomes ($p > 0.05$). This indicates that incretin-based therapies deliver reproducible efficacy across varied healthcare systems, despite differences in resource allocation, clinical infrastructure, and patient demographics. Such uniformity suggests that the mechanisms of incretin response—driven by receptor biology rather than environmental or ethnic variability—are broadly consistent across Latin American populations (ADA, 2025b; Lincoff et al., 2023).

From a policy perspective, this cross-country homogeneity holds critical implications. It underscores that access to incretin-based therapies, rather than biologic variability, is the principal determinant of outcome disparities in the region. These results advocate for regional integration of these therapies into public health frameworks addressing obesity, diabetes, and metabolic liver disease. Given the shared metabolic epidemiology across Latin America—where

T2DM prevalence exceeds 10% in urban populations—widespread implementation could yield significant reductions in healthcare costs associated with dialysis, cardiovascular events, and advanced liver disease (Levin et al., 2024; ADA, 2025a).

Mechanistic Integration: From Metabolism to Multiorgan Protection

This study's integrative outcomes highlight the unifying role of incretin biology across metabolic, cardiovascular, renal, and hepatic systems. The mechanisms underlying these pleiotropic benefits are multifactorial and interconnected. GLP-1 and GIP receptor activation enhances insulin sensitivity, suppresses appetite, and reduces systemic inflammation, leading to global metabolic stabilization. These actions collectively mediate improvements in endothelial function, oxidative stress, and tissue remodeling—pathways implicated in cardiovascular and renal disease progression (Kosiborod et al., 2023; Perkovic et al., 2024; Lincoff et al., 2023).

Furthermore, the convergence of benefits across organ systems supports a paradigm shift in endocrinology from "glucose-centric" to "systemic-metabolic" disease management. Incretin-based therapies represent not just pharmacologic innovation but a new physiologic strategy for restoring homeostasis in complex metabolic disorders. This approach aligns with the 2025 ADA Standards of Care, which emphasize personalized, weight-centered, and cardiometabolic-focused diabetes management (ADA, 2025a; ADA, 2025b).

Strengths, Limitations, and Future Directions

The strengths of this study include its large multicountry sample size, harmonized data collection, and comprehensive evaluation of multisystem outcomes. The consistent results across countries strengthen the external validity and demonstrate the feasibility of regional research collaborations in Latin America. However, limitations include potential selection bias toward patients receiving structured follow-up, as well as reliance on noninvasive measures for hepatic and renal assessment rather than histologic or imaging endpoints. Moreover, the study duration of 12 months, while adequate to detect intermediate outcomes, does not capture long-term event reduction.

Future research should focus on extending follow-up duration, incorporating longitudinal cardiovascular and renal endpoints, and exploring molecular markers predictive of differential response. In addition, the economic impact and cost-effectiveness of incretin therapies should be evaluated within the context of Latin American healthcare systems to support sustainable implementation and reimbursement policies.

This multicenter analysis confirms that incretin-based therapies represent a comprehensive metabolic intervention capable of transforming the management of obesity, T2DM, and related complications. The convergence of benefits across metabolic, cardiovascular, renal, and hepatic domains underscores their value as the cornerstone of modern endocrinology. Most importantly, the consistency of outcomes across Mexico, Colombia, and Ecuador demonstrates that these therapies are both biologically robust and regionally translatable. Their inclusion in national treatment algorithms offers a realistic path toward reducing the regional burden of chronic metabolic disease and achieving sustainable health gains consistent with the objectives of the World Health Organization and the 2030 Agenda for Sustainable Development.

5. Conclusión

The present multinational study consolidates evidence demonstrating that incretin-based therapies—both GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists—represent a paradigm shift in the management of metabolic disease. Across Mexico, Colombia, and Ecuador, these agents consistently produced clinically significant reductions in body weight, HbA1c, blood

pressure, and lipid parameters, alongside preservation of renal function and marked hepatic improvement. The uniformity of these outcomes across three distinct Latin American healthcare systems underscores the biological robustness and translatability of incretin pharmacology, validating its application beyond controlled trial environments.

From a clinical standpoint, the observed mean weight loss of approximately 10% and HbA1c reduction of 1.3 percentage points confirm that incretin-based therapies address the dual burden of obesity and T2DM with an efficacy unattainable by traditional glucose-lowering drugs. This dual mechanism—targeting both metabolic regulation and organ protection—positions incretin-based agents as the cornerstone of modern endocrinology (ADA, 2025a; Frías et al., 2021; Wilding et al., 2021). Furthermore, reductions in systolic and diastolic blood pressure, along with favorable shifts in lipid profiles, highlight their cardiovascular relevance, paralleling the outcomes of SELECT and SURPASS trials, where semaglutide and tirzepatide demonstrated significant reductions in major adverse cardiovascular events (Lincoff et al., 2023; Kosiborod et al., 2023).

Equally important are the renal and hepatic benefits documented in this cohort. The positive slope in eGFR (+2.3 mL/min/1.73 m^2) and regression of albuminuria categories reflect the renoprotective potential of these therapies, consistent with findings from FLOW and SURPASS-4 (Perkovic et al., 2024; Heerspink et al., 2022). These outcomes reinforce the KDIGO 2024 recommendations advocating GLP-1 receptor agonists as first-line therapy for patients with T2DM and CKD, in parallel with SGLT2 inhibitors (Levin et al., 2024). Likewise, the observed decline in hepatic fat content (−30 dB/m by CAP) and improvement in fibrosis indices (FIB-4, NFS) align with the NEJM 2021 semaglutide trial in NASH and the EASL–EASD–EASO 2024 guidelines endorsing incretin-based agents for MASLD treatment (Newsome et al., 2021; Tacke et al., 2024). These data confirm that incretin therapies provide multisystem protection, mitigating disease progression across metabolic, renal, cardiovascular, and hepatic axes.

The absence of significant intercountry differences ($p > 0.05$) across all endpoints provides compelling evidence that incretin pharmacotherapy delivers consistent efficacy independent of geographic or structural healthcare variability. This finding is of particular importance for Latin America, a region where the prevalence of obesity and diabetes continues to rise and access to specialized therapies remains uneven (ADA, 2025b). It emphasizes that the primary challenge is access and implementation, not biological responsiveness. Consequently, national and regional health authorities should prioritize the incorporation of incretin-based therapies into public health frameworks, as doing so could substantially reduce long-term healthcare costs by preventing complications such as dialysis-dependent kidney disease, heart failure, and cirrhosis.

At the translational level, these findings advance a new vision of endocrinology—one that integrates weight, metabolic control, and organ preservation as inseparable therapeutic goals. The capacity of incretin-based agents to unify treatment targets across multiple organ systems signals a move away from the glucose-centric paradigm toward comprehensive metabolic restoration. This aligns with the 2025 ADA Standards of Care, which emphasize a patient-centered, outcome-driven model focused on cardiovascular, renal, and hepatic health rather than isolated glycemic endpoints (ADA, 2025a).

From a regional perspective, the evidence presented here underscores an opportunity for Latin America to become a global model of integrated metabolic care. Implementing incretin-based therapies within preventive and primary care programs would directly support multiple Sustainable Development Goals (SDGs), including SDG 3 (Good Health and Well-being) and SDG 10 (Reduced Inequalities), by improving population health and reducing disparities in access to innovative treatment. Multisectoral collaboration between governments, academia, and the

pharmaceutical industry will be essential to ensure equitable availability and affordability of these therapies.

In conclusion, incretin-based therapies represent a metabolic revolution in modern medicine—one that redefines endocrinology through multi-organ, evidence-based, and globally applicable intervention. Their demonstrated efficacy across Mexico, Colombia, and Ecuador confirms that the future of metabolic disease management in Latin America lies not only in innovation, but in equitable implementation. By embracing incretin-based therapy as a cornerstone of chronic disease prevention, the region can advance toward a more sustainable, healthier, and scientifically integrated healthcare model.

Referencias Bibliográficas

Lincoff, A. M., et al. (2023). Semaglutide and cardiovascular outcomes in obesity without diabetes. The New England Journal of Medicine, 389(24), 2221–2232. https://doi.org/10.1056/NEJMoa2307563

Perkovic, V., et al. (2024). Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. The New England Journal of Medicine, 391(2), 109–121. https://doi.org/10.1056/NEJMoa2403347

Kosiborod, M. N., et al. (2023). Semaglutide in patients with heart failure with preserved ejection fraction and obesity. The New England Journal of Medicine, 389(12), 1069–1084. https://doi.org/10.1056/NEJMoa2306963

Wilding, J. P. H., et al. (2021). Once-weekly semaglutide in adults with overweight or obesity. The New England Journal of Medicine, 384(11), 989–1002. https://doi.org/10.1056/NEJMoa2032183

Rubino, D., et al. (2021). Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance (STEP 4). JAMA, 325(14), 1414–1425. https://doi.org/10.1001/jama.2021.3224

Garvey, W. T., et al. (2022). Two-year effects of semaglutide in adults with overweight or obesity (STEP 5). Nature Medicine, 28(10), 2083–2091. https://doi.org/10.1038/s41591-022-02026-4

Jastreboff, A. M., et al. (2022). Tirzepatide once weekly for the treatment of obesity (SURMOUNT-1). The New England Journal of Medicine, 387(3), 205–216. https://doi.org/10.1056/NEJMoa2206038

Malhotra, A., et al. (2024). Tirzepatide for the treatment of obstructive sleep apnea (SURMOUNT-OSA). The New England Journal of Medicine, 390(25), 2351–2364. https://doi.org/10.1056/NEJMoa2404881

Frías, J. P., et al. (2021). Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes (SURPASS-2). The New England Journal of Medicine, 385(6), 503–515. https://doi.org/10.1056/NEJMoa2107519

Heerspink, H. J. L., et al. (2022). Effects of tirzepatide versus insulin glargine on kidney outcomes in type 2 diabetes (SURPASS-4 post hoc). The Lancet Diabetes & Endocrinology, 10(11), 774–785. https://doi.org/10.1016/S2213-8587(22)00243-1

Wharton, S., et al. (2023). Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. The New England Journal of Medicine, 389(10), 877–888. https://doi.org/10.1056/NEJMoa2302392

Jastreboff, A. M., et al. (2023). Triple-hormone-receptor agonist retatrutide for obesity — A phase 2 trial. The New England Journal of Medicine, 389(6), 514–526. https://doi.org/10.1056/NEJMoa2301972

Frías, J. P., et al. (2023). Efficacy and safety of co-administered once-weekly cagrilintide and semaglutide (CagriSema) in type 2 diabetes. The Lancet, 402(10399), 1116–1128. https://doi.org/10.1016/S0140-6736(23)01163-7

Newsome, P. N., et al. (2021). A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. The New England Journal of Medicine, 384(12), 1113–1124. https://doi.org/10.1056/NEJMoa2028395

Knop, F. K., et al. (2023). Oral semaglutide 50 mg once per day in adults with overweight or obesity (OASIS-1). The Lancet, 402(10402), 203–216. https://doi.org/10.1016/S0140-6736(23)01185-6

American Diabetes Association Professional Practice Committee. (2025). 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2025. Diabetes Care, 48(Suppl. 1), S181–S206. https://doi.org/10.2337/dc25-S009

American Diabetes Association Professional Practice Committee. (2025). 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: Standards of Care in Diabetes—2025. Diabetes Care, 48(Suppl. 1), S167–S180. https://doi.org/10.2337/dc25-S008

Levin, A., et al. (2024). Executive summary of the KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International, 105(4S), S1–S69. https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2024-CKD-Guideline-Executive-Summary.pdf

Tacke, F., et al. (2024). EASL–EASD–EASO clinical practice guidelines on the management of MASLD. Journal of Hepatology, 81(2), 390–448. https://doi.org/10.1016/S0168-8278(24)00329-5

Abasheva, D., et al. (2024). GLP-1 receptor agonists in patients with chronic kidney disease. Clinical Kidney Journal, 17(Suppl. 2), ii19–ii35. https://doi.org/10.1093/ckj/sfae104

Acknowledgements

The authors would like to express their deepest gratitude to Dr. Jorge Ángel Velasco Espinal for his visionary leadership, guidance, and intellectual contribution throughout the conception, design, and development of this research. His commitment to advancing regenerative and ethical innovation in aesthetic medicine was fundamental to the realization of this work.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The work was fully supported by the institutional resources of the participating organizations.

Conflicto de Intereses: Los autores declaran que no tienen conflictos de intereses relacionados con este estudio y que todos los procedimientos seguidos cumplen con los estándares éticos establecidos por la revista. Asimismo, confirman que este trabajo es inédito y no ha sido publicado, ni parcial ni totalmente, en ninguna otra publicación.