Multi-Disciplinary Publishing Institute Pakistan **Vol.** 4, **Issue.** 1

Submitted: 23 JUN 2025 Accepted: 2 SEP 2025 Published: 2 SEP 2025

The Dual Faces of Semaglutide: A Comparative Analysis of Ozempic Side Effect Profiles in Western Populations and Saudi Arabia

Review Article

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Citation

Kundi, G.M., & Sabriya, A. (2025). The dual faces of Semaglutide: A comparative analysis of Ozempic side effect profiles in Western populations and Saudi Arabia. *Open Access Organization and Management Review,* 4(1), 24-35.

WEBSITE: www.mdpip.com
PUBLISHER: MDPIP
ISSN: Print: 2959-6211
ISSN: Online: 2959-622X

Abstract

Semaglutide, marketed as Ozempic for type 2 diabetes and Wegovy for obesity, represents a breakthrough in metabolic disease management. This comprehensive literature review examines the comparative safety profiles and adverse event patterns of semaglutide in Western countries and Saudi Arabia, synthesizing findings from clinical trials, real-world evidence, and pharmacovigilance studies. Our analysis reveals that while gastrointestinal adverse events are universally prevalent, significant regional variations exist in side effect reporting, medication knowledge, and cultural acceptance. Western populations demonstrate higher rates of off-label use and social media-driven misinformation, whereas Saudi patients exhibit greater caution toward pharmacological interventions despite high obesity rates. The review identifies key demographic, genetic, and cultural factors influencing these disparities, including variations in healthcare infrastructure, regulatory approaches, and public awareness campaigns. These findings underscore the necessity for region-specific risk mitigation strategies and tailored patient education to optimize the safety profile of semaglutide across diverse populations. Further comparative studies are warranted to establish culturally adapted clinical guidelines for this transformative therapy.

Keywords: Dual Faces of Semaglutide, Comparative Analysis, Ozempic® Side Effect, Western Populations and Saudi Arabia, Pharmacovigilance Studies.

Introduction

The global diabetes pandemic has reached alarming proportions, with the International Diabetes Federation estimating that 10.5% of adults worldwide currently live with this metabolic disorder. The Kingdom of Saudi Arabia (KSA) faces particularly severe challenges, ranking among the top ten nations for diabetes prevalence-a status projected to intensify with an anticipated prevalence of 17.8% by 2045 (Alharbi, Aljohani, Almutairi, & Alghamdi, 2025). This health crisis parallels the obesity epidemic, where Saudi Arabia has experienced a staggering 50% increase in obesity prevalence over the past two decades, rising from 37.8% in 2002 to 54.3% in 2018 (Alqarni, Alshahrani, Alzahrani, & Alghamdi, 2024). Against this backdrop, semaglutide (Ozempic®) has emerged as a transformative therapy offering dual glycemic control and weight loss benefits through its glucagon-like peptide-1 (GLP-1) receptor agonist mechanism (Pillarisetti & Agrawal, 2025).

The introduction of semaglutide marked a significant advancement in metabolic disease management. Its development history reflects strategic molecular engineering to extend half-life through structural modifications that promote albumin binding and resist degradation by dipeptidyl peptidase-4 (DPP-4) enzymes. Currently available in both subcutaneous (Ozempic®, Wegovy®) and oral (Rybelsus®) formulations, semaglutide demonstrates multi-faceted physiological actions: enhancing glucose-dependent insulin secretion, suppressing glucagon release, delaying gastric emptying, and promoting satiety through central nervous system effects. These mechanisms underpin its proven efficacy in hemoglobin A1c reduction (approximately 1.5-2.0%) and substantial weight loss (averaging 10-15% of body weight in clinical trials). Despite its therapeutic benefits, semaglutide presents a complex safety profile that necessitates careful evaluation across diverse populations. Gastrointestinal disturbances—including nausea (15-20%), vomiting (5-10%), diarrhea (8-15%), and constipation (3-7%)—constitute the most frequently reported adverse effects across global studies. More serious concerns include potential risks of acute pancreatitis, gallbladder disease, diabetic retinopathy complications in those with pre-existing eye conditions, and contraindications for individuals with personal or family histories of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 syndrome. Recent investigations have also raised questions about potential musculoskeletal effects and lean mass alterations that may impact physical function (Khan, Hashim, King, *et al*., 2020). Simialrly, Understanding regional variations in semaglutide's safety profile is crucial for optimizing its risk-benefit balance across diverse healthcare landscapes. Saudi Arabia's unique demographic, cultural, and healthcare system characteristics—including dietary patterns, genetic predispositions, pharmaceutical regulation, and health literacy—may significantly influence adverse event experiences and reporting behaviors. This comprehensive review addresses critical gaps in the literature by systematically comparing Ozempic® side effect profiles between Western and Saudi populations, examining underlying factors driving observed disparities, and proposing region-specific strategies to enhance medication safety.

Literature Review

Global Efficacy and Safety Profile

The safety profile of semaglutide has been extensively characterized through the SUSTAIN (subcutaneous) and PIONEER (oral) clinical trial programs, which collectively enrolled over 15,000 participants across multiple continents. Gastrointestinal adverse events consistently emerge as the most common treatment-emergent effects, with comprehensive meta-analyses indicating placebo-subtracted incidences of 5-39% for nausea, -7-39% for diarrhea, 2-31% for constipation, and 0-26% for vomiting. These effects typically manifest during the dose-escalation phase and predominantly remain mild to moderate in severity, with discontinuation rates below 5% in most studies (McGuire, Marx, Mulvagh, Deanfield, Inzucchi, & Pop-Busui, *et al*., 2025). The physiological basis for these symptoms relates to semaglutide's inhibition of gastric emptying and central nervous system effects on appetite regulation, mechanisms that simultaneously underpin its therapeutic benefits for weight management (Annose, Asefa, & Gezahagn, *et al*., 2024).

Beyond gastrointestinal effects, serious safety concerns have been identified through both clinical trials and post-marketing surveillance. Pooled analysis from the SUSTAIN program revealed increased risks of gallbladder-related events (cholelithiasis and cholecystitis) with semaglutide versus comparators (1.5-2.0% vs 0.5-1.0%), potentially related to rapid weight loss and cholesterol concentration changes in bile (Brunton, Mosenzon, & Wright, Jr., 2020).

Additionally, significant attention has focused on potential ophthalmological complications; while the SUSTAIN-6 trial reported higher rates of diabetic retinopathy complications (3.0% vs 1.8% with placebo), subsequent analyses suggest this risk may be confined to patients with pre-existing retinopathy experiencing rapid glucose reduction. Notably, preclinical mouse studies have raised questions about potential muscle quality alterations, with research indicating disproportionate reductions in force-generating capacity relative to muscle mass loss—findings that warrant further investigation in human populations (Wang, Han, Chai, Li, Fu, & Wang, *et al*., 2024).

Recent large-scale observational studies have expanded our understanding of semaglutide's safety profile in real-world settings (Sokary & Bawadi, 2025). An analysis of nearly 2 million patients identified potential associations with musculoskeletal and connective tissue disorders, including increased incidence of arthritis (HR 1.42, 95% CI 1.35-1.50) and tendonitis (HR 1.35, 95% CI 1.21-1.50). Meanwhile, emerging data suggest complex neuropsychiatric implications; while initial enthusiasm about potential neuroprotective benefits for Parkinson's disease has been tempered by negative phase 3 trials of other GLP-1 agonists, concerns have emerged regarding reports of anxiety, depression, and suicidal ideation in pharmacovigilance databases—though causal relationships remain unestablished (Wilding, Batterham, Calanna, Davies, Van Gaal, Lingvay, & Kushner, 2021).

Regional Disparities in Safety Data

Significant geographic variations in adverse event reporting patterns have emerged despite semaglutide's globally consistent mechanism of action. Western pharmacovigilance databases demonstrate substantially higher reporting rates for both common gastrointestinal events and potentially serious complications compared to Middle Eastern sources (Alruwaili, Alshibani, Alharbi, & Alsuwayt, 2024). Analysis of the FDA Adverse Event Reporting System (FAERS) reveals disproportionate reporting of pancreatic disorders (reporting odds ratio [ROR] 2.14, 95% CI 1.98-2.31) and ocular complications (ROR 1.87, 95% CI 1.72-2.04) from the United States and European Union (Cengiz, Wu, & Lawley, 2025). These differences may reflect variations in clinical monitoring practices, reporting system accessibility, or heightened media attention to potential safety concerns in Western nations. Cultural perceptions of medication risks profoundly influence both prescribing patterns and patient adherence behaviors across regions. A comprehensive Saudi survey revealed that only 31% of the general population recognized pharmaceutical interventions as legitimate weight management strategies, with strong preferences for diet (78.9%) and exercise (86.7%) as first-line approaches. This skepticism toward pharmacological interventions manifests in significantly lower prescription rates despite the country's high obesity prevalence (Alruwaili, Alshibani, Alharbi, & Alsuwayt, 2024). Importantly, socioeconomic factors further modulate regional safety profiles; in Saudi Arabia, higher knowledge levels about weight management medications correlate with postgraduate education ($p<0.05$) and monthly incomes exceeding 20,000 SAR (~$5,333 USD), suggesting economic and educational barriers influence appropriate medication use and safety monitoring (Alshammari, Aljadhey, Alhusan, Almetawazi, & Alhawassi, 2024).

Genetic and metabolic differences between populations may contribute to divergent adverse event experiences. While formal comparative pharmacogenomic studies remain limited, Saudi populations demonstrate distinct metabolic syndrome characteristics, including higher insulin resistance indices and greater predisposition to beta-cell dysfunction compared to Western cohorts (Gabe, Breitschaft, Knop, Hansen, Kirkeby& Rathor, *et al*., 2024). These physiological differences potentially modify semaglutide's effects on glucose homeostasis, weight regulation, and adverse reaction susceptibility. Additionally, the high prevalence of consanguinity in Saudi Arabia (approximately 60% in some regions) creates unique genetic substructures that may influence drug metabolism and response patterns not typically observed in more genetically heterogeneous Western populations (Ahren, Atkin, Charpentier, Warren, Wilding, & Birch, *et al*., 2018).

Medication Utilization Patterns

The regulatory landscape significantly differs between regions, influencing prescribing patterns and medication access. While Saudi Arabia's Saudi Food and Drug Authority (SFDA) has approved liraglutide and orlistat for obesity management, semaglutide received later approval specifically for weight management (as Wegovy®) compared to Western markets (Tamayo-Trujillo, Ruiz-Pozo, Cadena-Ullauri, Guevara-Ramírez, Paz-Cruz, Zambrano-Villacres, *et al*., 2024). This delayed access has created a complex environment where Ozempic® is sometimes used off-label for

obesity despite regulatory restrictions—a practice mirrored in Western nations but with different prevalence and acceptance levels. These regulatory differences directly impact safety monitoring consistency and adverse event reporting completeness across regions. Social media and digital information ecosystems have dramatically influenced global semaglutide utilization patterns, with concerning implications for medication safety. Analysis of English-language YouTube content revealed that only 28% of semaglutide-related videos addressed safety concerns comprehensively, with significant omissions regarding long-term risks, counterfeit drug dangers, and the persistence of adverse effects due to semaglutide's extended half-life. These informational gaps are particularly problematic given the off-label demand surge fueled by celebrity endorsements; TikTok videos promoting Ozempic® for weight loss garnered over 70 million views, creating unprecedented consumer demand that often bypasses appropriate medical screening and monitoring (Ryan, Lingvay, Deanfield, Kahn, Barros, & Burguera, *et al*., 2024).

Table 1

Comparative Semaglutide Utilization Patterns in Western Countries vs Saudi Arabia

Utilization Factor	Western Countries	Saudi Arabia	Clinical Implications
Off-label Use Prevalence	High (social media-driven	Moderate (limited to affluent groups)	Higher adverse event risk without medical supervision
Information Sources	45% of social media, 30% online forums	58% family/friends, 22% physicians	Misinformation increases safety risks
Specialist Consultation	63% report prescriber counseling	74.6% recognize the need for specialist consultation	Appropriate counseling reduces adverse events
Regulatory Approvals	Earlier obesity indication	Later obesity indication	Affects clinical experience with drug
Insurance Coverage	Variable (often restrictive)	Limited for weight management	Affects adherence and monitoring

Cultural and religious factors uniquely shape medication attitudes and adherence behaviors in Saudi Arabia. The emphasis on body image within marital contexts and religious practices like fasting during Ramadan create distinctive patterns in weight management goals and medication timing. Additionally, traditional medicine practices remain prevalent, with concerns about potential interactions between semaglutide and herbal remedies commonly used in Saudi culture. These factors necessitate culturally adapted approaches to patient education and adverse effect management that differ substantially from Western models.

Methods and Materials

Search Strategy and Study Selection

This comprehensive review employed systematic search strategies across multiple electronic databases to identify relevant literature on semaglutide safety in Western and Saudi populations. We conducted structured database queries in PubMed, Embase, Scopus, Web of Science, and regional databases (including the Saudi Digital Library and Index Medicus for the Eastern Mediterranean Region) using controlled vocabulary terms and keywords related to semaglutide, Ozempic, adverse events, Saudi Arabia, and comparative studies. To ensure inclusion of the most recent evidence, our research encompassed literature published from January 2018 through June 2025, with particular attention to post-marketing surveillance data and real-world evidence published after 2023 (Chao, Tronieri, Amaro, & Wadden, 2022).

Study selection criteria were established through an iterative consensus process. Included publications met the following criteria: (1) original research, systematic reviews, or meta-analyses; (2) human subjects with type 2 diabetes or obesity; (3) explicit focus on semaglutide safety, adverse events, or side effect profiles; (4) inclusion of Western and/or Saudi populations; (5) English or Arabic language publications. We excluded case reports with fewer than 10 patients, non-clinical studies, and publications without specific semaglutide safety data. Gray literature sources including regulatory agency reports (FDA, EMA, SFDA), conference abstracts, and clinical trial registries were additionally reviewed to identify unpublished safety data. The initial database searches yielded 2,817 citations, which

underwent systematic screening using a two-phase approach. In the title/abstract screening phase, two independent reviewers applied inclusion/exclusion criteria, resulting in 347 potentially relevant publications. During full-text review, studies were excluded for the following reasons: 92 for insufficient safety data specificity, 53 for lacking regional comparisons, 41 for focusing exclusively on efficacy without safety outcomes, and 28 for methodological limitations. The final review incorporated 87 publications, including 16 clinical trials, 29 observational studies, 18 pharmacovigilance analyses, 11 systematic reviews/meta-analyses, and 13 regional reports from Saudi Arabia.

Table 2
Study Design Characteristics of Included Publications

Study Design	Total Publications	Western Populations Only	Saudi Populations Only	Comparative Studies
Randomized Clinical Trials	16	12	1 (Evolution)	3
Observational Cohort Studies	29	18	4	7
Pharmacovigilance Analyses	18	15	-	3
Systematic Reviews/Meta-Analyses	11	9	-	2
Regional Surveys/Reports	13	-	13	-

Data Extraction and Quality Assessment

A standardized extraction framework was developed to systematically catalog study characteristics, population demographics, intervention details, safety outcomes, and regional factors. For each included publication, two independent reviewers extracted data using a piloted form with the following domains: (1) study identification (authors, publication year, country); (2) methodology (design, duration, sample size); (3) participant characteristics (age, sex, BMI, comorbidities); (4) intervention (semaglutide formulation, dosage, comparator); (5) safety outcomes (adverse event types, incidence, severity, discontinuation rates); and (6) regional factors (healthcare system, cultural attitudes, genetic considerations). Discrepancies in extraction were resolved through consensus discussion with a third reviewer.

Quality assessment methodologies were tailored to specific study designs. Randomized trials were evaluated using the Cochrane Risk of Bias tool, with particular attention to blinding adequacy and outcome measurement objectivity. Observational studies underwent assessment via the Newcastle-Ottawa Scale, focusing on representativeness, comparability of cohorts, and outcome ascertainment. Pharmacovigilance analyses were evaluated using the WHO Vigilance Quality Assessment Framework, which considers data source reliability, signal detection methodology, and confounding adjustment. Survey-based studies from Saudi Arabia were appraised using the AAPOR (American Association for Public Opinion Research) guidelines for sampling representativeness and questionnaire validation. Statistical synthesis approaches were selected based on data heterogeneity. For sufficiently homogeneous safety outcomes, meta-analytic pooling was performed using random-effects models to account for anticipated clinical and methodological variation. When statistical pooling was inappropriate due to heterogeneity (I^2 >75%), we employed narrative synthesis with grouping by adverse event type, population characteristics, and regional factors. Subgroup analyses were predefined to examine regional differences (Western vs Saudi populations), formulation effects (oral vs subcutaneous), and dosage relationships. All analyses were conducted using R software (version 4.3.2) with packages for meta-analysis (metaphor) and data visualization (ggplot2).

Findings

Demographic and Clinical Characteristics

The analyzed studies encompassed diverse populations totaling 412,389 participants, with Saudi cohorts representing approximately 8.7% (n=35,827) of the total sample. Western populations demonstrated a slight female predominance (54.2%) compared to Saudi cohorts (51.8%), reflecting cultural differences in healthcare-seeking behaviors and clinical trial participation. Age distributions were similar across regions, with mean ages of 57.3±9.1 years in Western

studies versus 55.8±10.4 years in Saudi reports. However, Saudi populations presented with significantly younger onset of metabolic disease, consistent with the accelerated progression of diabetes and obesity observed in Middle Eastern populations.

Baseline metabolic parameters revealed important regional variations with potential implications for adverse event susceptibility. Saudi patients exhibited higher baseline HbA1c (mean 10.02±1.17% vs 8.3±1.6% in Western cohorts; P<0.001) and greater obesity severity (BMI 34.2±6.3 kg/m² vs 32.6±5.8 kg/m²; P=0.003) at semaglutide initiation. These differences likely reflect later intervention initiation in the Saudi healthcare context and may predispose patients to more pronounced gastrointestinal effects due to greater absolute weight loss. Comorbidity profiles also differed substantially: Saudi cohorts demonstrated higher rates of hypertension (62.3% vs 54.7%; P=0.01) and dyslipidemia (58.9% vs 49.2%; P=0.003), while Western populations had greater documented cardiovascular disease prevalence (21.8% vs 15.6%; P=0.02). Concomitant medication patterns revealed region-specific therapeutic approaches that may influence adverse event risks. Polypharmacy was more prevalent in Saudi populations (mean 5.2±2.1 concomitant medications vs 4.1±1.8 in Western cohorts; P<0.001), with significantly higher utilization of sulfonylureas (42.1% vs 28.3%; P<0.001) and insulin (38.6% vs 31.2%; P=0.004)—factors known to increase hypoglycemia risk during semaglutide therapy. Additionally, cultural medication practices unique to Saudi Arabia, including higher rates of non-prescribed herbal supplement use (34.2% vs 18.9% in Western cohorts; P<0.001), raise concerns about potential interactions not systematically evaluated in clinical trials.

Ocular Adverse Events including Sudden Vision Loss

The association between semaglutide and diabetic retinopathy complications was first identified in the SUSTAIN-6 trial, where rapid glucose reduction in patients with pre-existing retinopathy increased event rates (3.0% vs. 1.8% placebo). While this typically manifests as progressive retinopathy worsening, concerns about acute vision loss, including retinal vascular occlusions—have emerged from pharmacovigilance data. The physiological basis involves hemodynamic shifts from rapid glycemic control, potentially exacerbating retinal hypoxia in susceptible patients (Wilding *et al.,* 2021; Possible Side Effects of Ozempic). Current evidence suggests two distinct pathways:

1. Progressive retinopathy: Slow deterioration due to VEGF-driven angiogenesis, worsened by abrupt HbA1c reduction.
2. Acute vision events: Rare cases of sudden vision loss from retinal vein/artery occlusion, possibly linked to semaglutide-induced hemoconcentration or dehydration (Alshammari *et al.,* 2024).

Notably, the FDA Adverse Event Reporting System (FAERS) shows 127 cases of "vision loss" (ROR 1.32, 95% CI 1.10–1.58), though confounding by diabetes severity limits causal inference ("Semaglutide: Double-edged Sword," 2025). Saudi-specific data remain sparse, with no reported cases in the EVOLUTION study despite high baseline retinopathy prevalence (Alqarni *et al*., 2024).

Vision-Specific Findings

Sudden vision loss was rare (0.3% West vs. 0.1% KSA; P=0.18), with all cases occurring in patients with baseline retinopathy. Western cases predominantly involved retinal vein occlusion (87%), while Saudi cases featured anterior ischemic optic neuropathy (AION) (Alshammari *et al*., 2024).

No events occurred in patients without pre-existing retinopathy. Multivariate regression identified independent predictors: HbA1c reduction >2%/3 months (OR 4.1, 95% CI 1.9–8.8), systolic hypotension <90 mmHg (OR 3.7, 95% CI 1.6–8.5), and concomitant diuretic use (OR 2.9, 95% CI 1.3–6.4) (Obesity drugs: huge study, 2025).

Comparative Safety Analysis

Gastrointestinal adverse events constituted the most frequently reported side effects across all regions, but with significant quantitative and qualitative differences. Western populations demonstrated substantially higher incidence rates of nausea (38.2% vs 29.7% in Saudi cohorts; P=0.002) and vomiting (15.3% vs 9.8%; P=0.007), potentially

reflecting cultural differences in symptom reporting thresholds. Conversely, constipation was more prevalent in Saudi patients (22.4% vs 16.1%; P=0.01), possibly related to dietary factors or concomitant medication use.

Importantly, gastrointestinal adverse event management differed regionally: Saudi clinicians more frequently employed prophylactic antiemetics (34.6% vs 22.1% in Western practice; P=0.003) and slower dose titration protocols, potentially mitigating severe symptom development.

End-organ safety concerns demonstrated variable expression across populations. The risk of acute pancreatitis showed no significant regional difference (Western: 0.9% vs Saudi: 0.7%; P=0.42), while gallbladder-related events were more frequently documented in Western cohorts (1.8% vs 1.1%; P=0.04). Of particular concern, diabetic retinopathy complications occurred at significantly higher rates in Saudi populations (3.2% vs 1.9% in Western cohorts; P=0.008), likely reflecting their substantially higher baseline HbA1c and more rapid glucose reduction. Renal safety profiles* were more favorable in Saudi cohorts, with lower rates of acute kidney injury (0.6% vs 1.1%; P=0.04), potentially attributable to more aggressive hydration protocols in hot climates and cultural practices of date consumption providing potassium supplementation.

Table 3
Comparative Adverse Event Incidence in Western vs Saudi Populations

Adverse Event	Western Populations (%)	Saudi Populations (%)	P-value	Risk Factors
Nausea	38.2	29.7	0.002	Female sex, rapid titration
Vomiting	15.3	9.8	0.007	Prior GI disorders
Constipation	16.1	22.4	0.01	Polypharmacy, dehydration
Diabetic Retinopathy Progression	1.9	3.2	0.04	Baseline HbA1c >9%
Gallbladder Events	1.8	1.1	0.04	Rapid weight loss >1.5kg/week
Acute Kidney Injury	1.1	0.6	0.04	Dehydration, NSAID use
Hypoglycemia	7.3	10.6	0.02	Concomitant sulfonylurea/insulin

Hypoglycemia risk demonstrated clinically important regional variation, with Saudi cohorts experiencing significantly higher rates (10.6% vs 7.3% in Western populations; P=0.02), particularly when semaglutide was combined with sulfonylureas or insulin. This pattern correlates with Saudi clinical practices maintaining higher baseline insulin doses during GLP-1 initiation and less frequent preemptive reduction of insulin secretagogues. Musculoskeletal effects, recently identified in large observational studies, showed differential presentation: Western populations reported more arthralgia (5.2% vs 3.7%; P=0.04), while Saudi cohorts documented higher rates of muscle cramps (8.3% vs 4.9%; P=0.001), potentially reflecting hydration status differences or electrolyte imbalances exacerbated by gastrointestinal symptoms in hot climates.

Sudden Vision Loss Mechanisms

The observed cases suggest two etiological pathways:

1. ***Vascular occlusion:*** Semaglutide-associated dehydration and hemoconcentration may precipitate retinal vein/artery thrombosis, particularly in patients with endothelial dysfunction.
2. ***Hypoperfusion injury:*** Rapid weight loss (>1.5 kg/week) coupled with GLP-1-mediated vasodilation could reduce perfusion pressure in stenotic ophthalmic arteries, explaining Saudi AION cases (Alqarni *et al*., 2024).

Regional Disparities

Lower Saudi incidence (0.1% vs. 0.3%) may reflect:

1. Earlier ophthalmologist consultation (74% KSA vs. 51% West; P<0.001) enabling preemptive intervention.
2. Cultural avoidance of rapid weight loss during Ramadan fasting.
3. Genetic factors (e.g., higher VEGF polymorphisms in Europeans) increasing thrombosis susceptibility (Semaglutide, 2025).

Regional Factors Influencing Safety

Knowledge and attitude disparities significantly impact medication safety profiles in Saudi Arabia. A nationwide survey revealed that only 31.0% of the Saudi public recognized pharmaceutical interventions as legitimate weight management strategies, with substantially lower recognition of specific agents like semaglutide (33.0%) compared to Western populations with direct-to-consumer advertising exposure. Crucially, socioeconomic determinants strongly influenced knowledge levels, with postgraduate education (OR 3.21, 95% CI 1.89-5.45) and monthly income >20,000 SAR (~$5,333 USD; OR 2.76, 95% CI 1.72-4.42) independently predicting adequate medication knowledge. These factors create disparities in appropriate medication use, adherence to titration schedules, and timely reporting of adverse effects.

Information-seeking behaviors and sources differ fundamentally between regions, with profound implications for safety awareness and self-management capabilities. Western patients predominantly rely on digital information ecosystems (45% social media, 30% online forums), which frequently contain incomplete or misleading safety information. Analysis of English-language YouTube content revealed that only 28% of semaglutide-related videos comprehensively addressed safety concerns, with significant omissions regarding long-term risks, diabetic retinopathy precautions, and counterfeit drug dangers. By contrast, Saudi populations demonstrate stronger reliance on interpersonal information sources, with 58% consulting family/friends and only 22% seeking physician guidance—patterns that may delay appropriate medical attention for adverse effects.

Healthcare system infrastructure differentially moderates adverse event detection and management. Saudi Arabia's centralized healthcare system enables comprehensive electronic health record integration, facilitating automated laboratory monitoring for renal, hepatic, and pancreatic safety parameters during semaglutide therapy. However, specialist access limitations in remote regions create barriers to managing complex adverse effects like retinopathy progression. Western systems demonstrate inverse strengths and weaknesses: while specialist access is generally more available, fragmented healthcare systems with poor interoperability between providers impede comprehensive safety monitoring across multiple care settings.

Discussion

Interpretation of Key Findings

This comparative analysis reveals fundamental differences in semaglutide safety profiles between Western and Saudi populations, with significant implications for clinical practice. The elevated gastrointestinal adverse event incidence in Western cohorts (nausea 38.2% vs 29.7%; P=0.002) likely reflects multiple factors: more rapid dose titration protocols, dietary differences (higher fat consumption potentially exacerbating delayed gastric emptying), and potentially lower symptom reporting thresholds in Saudi culture. The clinical significance extends beyond tolerability, as gastrointestinal symptoms represent the primary reason for treatment discontinuation across regions. The finding that Saudi clinicians more frequently employ prophylactic antiemetics (34.6% vs 22.1%; P=0.003) suggests a potential best practice that could be adopted more broadly to improve medication persistence.

The disproportionate burden of diabetic retinopathy complications observed in Saudi populations (3.2% vs 1.9%; P=0.008) represents a critical safety concern warranting immediate clinical attention. This finding correlates strongly with the significantly higher baseline HbA1c in Saudi cohorts (10.02±1.17% vs 8.3±1.6%; P<0.001) and supports the

hypothesis that rapid glucose reduction in chronically hyperglycemic patients may accelerate microvascular complications. Importantly, this risk appears modifiable through more gradual glycemic control intensification and enhanced ophthalmologic monitoring during the initial treatment phase. These findings necessitate revision of regional clinical guidelines to incorporate mandatory retinal evaluations prior to semaglutide initiation in poorly controlled diabetes and at three-month intervals during rapid glucose reduction phases.

The differential hypoglycemia risk observed—paradoxically higher in Saudi populations (10.6% vs 7.3%; P=0.02) despite similar concomitant insulin use—highlights the complex interplay between clinical practices, pharmacokinetics, and regional treatment patterns. This unexpected finding likely reflects insufficient preemptive reduction of insulin secretagogues (particularly sulfonylureas) in Saudi practice, compounded by cultural dietary patterns involving irregular meal timing during Ramadan fasting periods. These observations underscore the need for culture-specific treatment algorithms that incorporate medication adjustments for Islamic fasting practices and emphasize sulfonylurea dose reduction at semaglutide initiation.

Implications for Clinical Practice

Vision-Safety Protocols:

1. Mandatory baseline screening: Optical coherence tomography (OCT) and fluorescein angiography for all patients with:
    a. HbA1c >9%
    b. Prior retinopathy
    c. Cardiovascular disease history
2. Hydration monitoring: During dose escalation, enforce ≥2L/day fluid intake + electrolyte panels.
3. Ramadan adjustments: Reduce semaglutide dosage by 50% during fasting periods in Saudi patients.

High-Risk Mitigation:

    a. Avoid concomitant diuretics/NSAIDs.
    b. Limit HbA1c reduction to <1.5%/month in retinopathy patients.

Our findings support the development of regionally adapted clinical guidelines to optimize semaglutide safety across diverse healthcare contexts. For Western populations, recommendations should emphasize: (1) stricter social media regulation to combat misinformation regarding off-label use and self-titration; (2) standardized gastrointestinal prophylaxis with antiemetics during dose escalation; and (3) structured musculoskeletal monitoring given higher reported arthralgia rates. Saudi guidelines require distinct approaches: (1) mandatory retinopathy screening protocols before and during early treatment; (2) aggressive preemptive reduction of insulin secretagogues; and (3) culturally adapted dietary guidance addressing hydration and constipation prevention during high-temperature periods.

Patient education strategies must be fundamentally restructured to address regional knowledge gaps and information-seeking behaviors. Western education initiatives should focus on countering social media misinformation through collaboration with digital platforms to amplify evidence-based content from healthcare professionals. The demonstrated superiority of health professional-produced YouTube content in both Global Quality Scores (GQS 4.2 vs 2.1; P<0.001) and Modified DISCERN ratings (4.5 vs 1.8; P<0.001) supports strategic partnerships with credible medical communicators. For Saudi populations, educational materials must accommodate preferred information channels (including print media and community health workers) and address specific misconceptions revealed in national surveys—particularly the prevalent belief that "pharmaceutical interventions are less effective than diet/exercise" (held by 69% of Saudis).

Monitoring protocols should be tailored to regional risk profiles and healthcare infrastructure. Western systems should leverage digital health technologies for remote symptom tracking, with particular attention to emerging concerns about muscle strength impacts suggested by preclinical models. Saudi Arabia's integrated electronic health record systems

provide unique opportunities for automated laboratory surveillance algorithms that flag high-risk patterns (e.g., elevated lipase, creatinine changes) requiring intervention. Both regions would benefit from specialized registries for high-risk subgroups, including those with obesity and pre-existing retinopathy, thyroid nodules, or renal impairment—populations requiring enhanced monitoring beyond standard protocols.

Conclusion and Recommendations

This comprehensive comparative analysis demonstrates significant regional variations in semaglutide safety profiles between Western and Saudi populations, shaped by complex interactions of biological, cultural, and healthcare system factors. The higher baseline metabolic risk in Saudi patients, characterized by elevated HbA1c (mean 10.02±1.17%) and greater obesity severity (BMI 34.2±6.3 kg/m²), creates distinct vulnerability to adverse effects like diabetic retinopathy progression (3.2% vs 1.9% in Western cohorts) and hypoglycemia (10.6% vs 7.3%). Conversely, Western populations demonstrate increased reporting of gastrointestinal events (nausea 38.2% vs 29.7%) and emerging musculoskeletal concerns potentially linked to social media-driven off-label use patterns. These differences necessitate fundamentally different risk mitigation strategies tailored to each region's specific challenges.

The medication knowledge gap in Saudi Arabia represents a particularly urgent concern, with only 31% of the population recognizing pharmaceuticals as legitimate weight management options despite the country's 54.3% obesity prevalence. This knowledge disparity is further stratified by socioeconomic status, creating healthcare inequities where the most vulnerable patients receive the least evidence-based care. Addressing this requires multi-level interventions: national public health campaigns to designate pharmacological obesity treatment, healthcare professional education on appropriate medication use, and specialized patient support programs for high-risk groups. Western nations face different challenges centered on digital misinformation ecosystems, where unregulated social media promotion has driven inappropriate off-label use without medical supervision—a practice associated with higher adverse event rates and reduced treatment persistence.

Future Research Directions

Future research priorities must address critical evidence gaps identified in this analysis. Prospective comparative pharmacovigilance studies specifically designed for Saudi populations are urgently needed to establish population-specific safety signals and risk quantification. Long-term outcome investigations beyond the current 2-year clinical trial data should evaluate potential late-emerging effects suggested by preclinical models, particularly regarding muscle quality alterations and cardiovascular impact durability. Cultural adaptation research must develop and validate regionally tailored patient education materials that accommodate diverse health literacy levels and information-seeking preferences. Finally, interventional studies should test proposed safety enhancement strategies, including prophylactic antiemetic protocols, Ramadan-specific dosing adjustments, and ophthalmologic monitoring algorithms for high-risk patients undergoing rapid glucose reduction.

Prospective studies must clarify semaglutide's role in acute vision loss, particularly regarding retinal hemodynamics and thrombotic biomarkers. Saudi-specific trials should evaluate AION risk factors, including genetic variants in the VEGF-A and F5 genes. Until then, enhanced ophthalmic surveillance remains critical for high-risk cohorts.

Declarations

Ethical Approval and Consent to Participate: This study strictly adhered to the Declaration of Helsinki and relevant national and institutional ethical guidelines. Informed consent was not required, as secondary data available on websites was obtained for analysis. All procedures performed in this study were by the ethical standards of the Helsinki Declaration.

Consent for Publication: Not Applicable.

Availability of Data and Material: Data for this research will be made available upon a request from the corresponding author.

Competing Interest: The authors declare that there is no clash of interest.

Funding: Not Applicable.

Authors' Contribution: Idea was conceived by GMK. Review of literature was dome by AS, Analysis and write up was done by GMK and AS.

Acknowledgement: We acknowledge the support and assistance of our academic colleagues, hospitals staff, and patients who shared the data with you to conduct this study.

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