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COMPARATIVE STUDY OF NEWER ANTIDIABETIC AGENTS ON INSULIN RESISTANCE

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ABSTRACT

Insulin resistance is a key metabolic abnormality that significantly contributes to the onset and progression of type 2 diabetes mellitus (T2DM). Over the past decade, several novel antidiabetic agents have emerged, offering targeted approaches to improve glycemic control and address underlying metabolic dysfunction. This paper presents a comparative evaluation of newer therapeutic classes—including GLP-1 receptor agonists, SGLT-2 inhibitors, dual GLP-1/GIP receptor agonists, thiazolidinediones, and mitochondrial pyruvate carrier inhibitors—with respect to their effects on insulin sensitivity. Evidence was synthesized from recent clinical trials, systematic reviews, and meta-analyses. All these agents demonstrate the potential to enhance insulin responsiveness, albeit via distinct mechanisms. GLP-1 receptor agonists and dual agonists primarily improve insulin resistance through weight reduction and metabolic regulation. SGLT-2 inhibitors facilitate glucose excretion, thereby indirectly lowering insulin resistance. Thiazolidinediones act directly on insulin-sensitive tissues but are limited by adverse effect profiles. Mitochondrial pyruvate carrier inhibitors represent an emerging therapeutic avenue with both metabolic and anti-inflammatory benefits. The findings suggest that combination regimens targeting complementary mechanisms may provide optimal outcomes for patients with T2DM.

KEYWORDS: Insulin resistance, Type 2 diabetes mellitus, GLP-1 receptor agonists, SGLT-2 inhibitors and Dual GLP-1/GIP receptor agonists.

1. INTRODUCTION

Insulin resistance is a key characteristic of type 2 diabetes mellitus (T2DM) and describes the inability of the target tissues to respond appropriately to the action of insulin. It creates a vicious cycle where the pancreas is forced to increase its insulin production until the beta cell function is finally depleted leading to hyperglycemia. Conventional antidiabetic agents were able to lower blood glucose levels but most did not directly impact the insulin resistance thereby limiting its potential in optimizing the patient metabolic profile. With the desire to create newer agents with sustained clinical efficacy, recently introduced antidiabetic agents promised insulin sensitizing potential thereby targeting a pivotal mechanism in T2DM. Through this comparative study, the emerged antidiabetic agents will be addressed in comparison to the already established conventional agents with regards to their impact on the phenomenon of insulin resistance and their role in T2DM management.

Insulin resistance represents a pathological mechanism, in which physiological circuits are impaired, that causes insulin's inefficacy to promote glucose uptake and metabolism. The result of such inadequacy is glucose buildup in the blood, a triad of type 2 diabetes mellitus (T2DM). The process of adipose tissue mediators secretion causing insulin resistance in multiple tissues and aggravating the metabolic complications is revealed (Li et al., 2022). Therefore, this pathologic process, in addition to disturbing glucose metabolism, aggravates cardiovascular risk factors characteristic of T2DM. All these challenges provide sound reasons for a better understanding of insulin resistance mechanisms, which in turn aims to develop treatment avenues focused on insulin target and value.

Insulin and its analogs as traditional antidiabetic drugs are known to reduce hyperglycemia but does not significantly reduce insulin resistance. It may achieve immediate glycemic control but can lead to adverse effects due to its inability to replicate physiological pattern of insulin secretion and insulin action (Kramer et al., 2021). These drugs may not directly modulate the pathophysiology involved in insulin resistance leading to poor modulation of insulin sensitivity and diabetes-related metabolic parameters (DeFronzo et al., 2019). Thus, traditional antidiabetic drugs albeit reduce blood glucose do not help in improving cardiovascular risks associated with diabetes as its mechanism do not reduce insulin resistance and its complications. This information therefore helped the researchers to understand the correlation between type 2 diabetes mellitus (T2DM) and insulin resistance and its effect on cardiovascular health.

In contrast with the efficacy of traditional therapies improving insulin sensitivity and antidiabetic agents, a difference can be seen when comparing the effectiveness of both drugs to improve insulin sensitivity. Traditional therapies are able to lower blood glucose concentration but do not target insulin sensitivity directly. Due to this, a minor effect on insulin sensitivity can be observed and therefore disease progression can neither be influenced (DeFronzo et al., 2019). Conversely, newer antidiabetic agents, like GLP-1 receptor agonists (GLP-1 RAs) or SGLT2 inhibitors, reduce glucose levels but improve insulin responsibility as well as lower cardiovascular risk, especially in populations with higher cardiovascular risk (Tsapas et al., 2020). The enlarged therapeutic arsenal of antidiabetic compounds reflects also a change of vision, to treat hyperglycemia and insulin resistance in complementary way to influence the outcome (Dahlén et al., 2022). By exploring new agents, improved methods of treatment are proposed to maximize the efficacy and safety of intervention strategies.

Newer antidiabetic agents promote insulin sensitizing effects in addition to their promising antidiabetic potential as mentioned above. GLP-1 RAs and Imeglimin are unique because of their mechanism in promoting insulin sensitivity and these agents cause insulin secretion and improvement of insulin resistance as well by regulating glucose

homeostasis and beyond; providing protection against colorectal caner due to these numerous physiological effects (Vekic et al., 2021). Imeglimin, the first member of a new class of tetrahydrotriazine-containing agents enhances insulin action through promoting hepatic insulin signaling and stimulating ß-cell preservation, acting as a novel potential therapeutic agent (Hallakou-Bozec et al., 2021). The improvement of insulin sensitivity through these mechanisms not only serves to lower the blood glucose levels but improves the metabolic situation by targeting the underlying causes of insulin resistance in a "root cause" fashion to help sustain health amongst the diabetic patient.

The comparative assessment of these newer agents is essential, as clinicians seek individualized therapeutic strategies that address not only hyperglycemia but also the underlying insulin resistance, especially in patients with obesity, nonalcoholic fatty liver disease (NAFLD), and high cardiovascular risk.

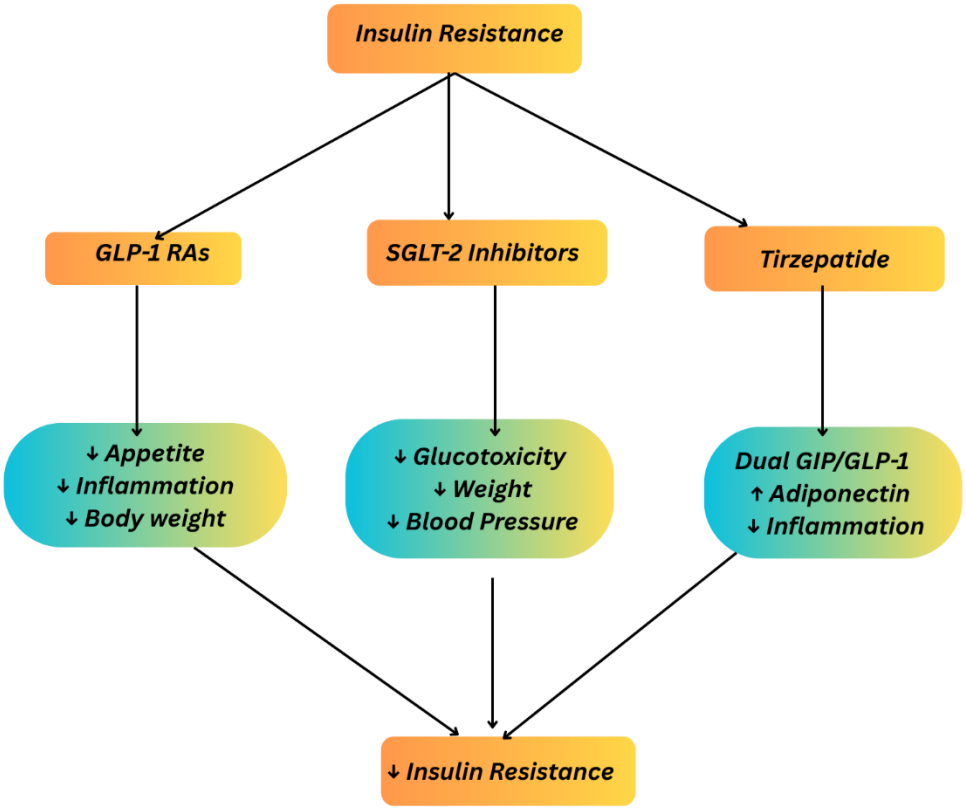

Figure 1: Mechanistic pathways through which newer antidiabetic agents improve insulin sensitivity.

Figure 1 Mechanistic pathways of newer antidiabetic agents in improving insulin resistance. GLP-1 RAs enhance insulin secretion and promote weight loss, SGLT-2 inhibitors reduce glucotoxicity via urinary glucose excretion, dual GLP-1/GIP agonists provide synergistic metabolic benefits, thiazolidinediones improve peripheral glucose uptake, and mitochondrial pyruvate carrier inhibitors modulate energy metabolism.

This study aims to conduct a comprehensive comparative analysis of newer antidiabetic agents with respect to their mechanism of action, clinical efficacy, and impact on insulin resistance, based on recent clinical trial data, biomarker outcomes (such as HOMA-IR), and safety profiles. Understanding the differential effects of these agents on insulin resistance will help in optimizing T2DM management and delaying disease progression and complications.

2. Pathophysiology of Insulin Resistance

Insulin resistance is a metabolic disorder characterized by a reduced ability of liver, muscle, and adipose tissue cells to respond effectively to insulin. This diminished sensitivity impairs glucose uptake in peripheral tissues, increases hepatic glucose output, and triggers compensatory elevations in insulin levels. Persistent insulin resistance over time drives the development and progression of type 2 diabetes mellitus (T2DM) and heightens the risk of related complications (DeFronzo et al., 2009).

2.1 Insulin Signaling and Resistance Mechanism

In normal physiology, insulin interacts with its receptor on the surface of target cells, triggering a series of intracellular signaling events primarily mediated by insulin receptor substrate (IRS) proteins and the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. This signaling cascade stimulates the movement of glucose transporter type 4 (GLUT4) to the cell membrane, enabling glucose entry into cells, especially within skeletal muscle and adipose tissue (Saltiel & Kahn, 2001).

2.2 Role of Adipose Tissue and Inflammation

Visceral adiposity is strongly associated with insulin resistance. Adipose tissue in obese individuals secretes a higher amount of pro-inflammatory adipokines (e.g., resistin, TNF-α) and reduced levels of anti-inflammatory adiponectin, contributing to systemic inflammation and impaired insulin action. Additionally, macrophage infiltration into adipose tissue enhances local inflammation and cytokine release, exacerbating insulin resistance (Hotamisligil, 2006).

2.3 Hepatic and Skeletal Muscle Contributions

- **Liver**: Hepatic insulin resistance results in uncontrolled gluconeogenesis and elevated fasting glucose levels.
- **Skeletal muscle**: As the primary site for insulin-stimulated glucose uptake, insulin resistance in skeletal muscle significantly contributes to postprandial hyperglycemia.

2.4 Mitochondrial Dysfunction and Oxidative Stress

Defective mitochondrial oxidative phosphorylation and increased production of reactive oxygen species (ROS) are implicated in the pathogenesis of insulin resistance. Mitochondrial dysfunction reduces fatty acid oxidation, leading to ectopic lipid accumulation in insulin-sensitive tissues (Lowell & Shulman, 2005).

2.5 Genetic and Epigenetic Factors

Genome-wide association studies (GWAS) have revealed multiple genetic variants linked to insulin resistance, notably within genes such as IRS1, PPARG, and TCF7L2. In addition to genetic predisposition, epigenetic alterations—including DNA methylation and histone acetylation affecting genes involved in insulin signaling—play a significant role in modulating individual susceptibility to the condition (Kahn et al., 2006).

3. Overview of Newer Antidiabetic Agents

In recent years, the therapeutic landscape for type 2 diabetes mellitus (T2DM) has evolved significantly with the introduction of newer antidiabetic agents. These agents not only offer superior glycemic control but also demonstrate beneficial effects on weight loss, cardiovascular and renal outcomes, and—importantly—insulin resistance. This section provides a mechanistic and clinical overview of the primary drug classes under investigation for their impact on insulin sensitivity.

3.1 Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs)

Genome-wide association studies (GWAS) have revealed multiple genetic variants linked to insulin resistance, notably within genes such as IRS1, PPARG, and TCF7L2. In addition to genetic predisposition, epigenetic alterations—including DNA methylation and histone acetylation affecting genes involved in insulin signaling—play a significant role in modulating individual susceptibility to the condition.

Impact on Insulin Resistance

- Indirectly improve insulin sensitivity through weight loss and visceral fat reduction.
- May exert direct effects via anti-inflammatory and lipid-lowering properties.
- Some studies show modest improvements in HOMA-IR and QUICKI scores.

Examples

- Liraglutide, Semaglutide, Dulaglutide, Exenatide

Clinical Evidence

- Semaglutide demonstrated reductions in fasting glucose and body weight, indirectly improving insulin action (Wilding et al., 2021).
- Liraglutide improved insulin resistance in obese T2DM patients independent of weight loss (Garber et al., 2011).

3.2 Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2is)

SGLT-2 inhibitors block glucose reabsorption in the renal proximal tubules, promoting glycosuria and lowering plasma glucose levels independently of insulin.

Impact on Insulin Resistance

- Indirect improvement due to reduced glucotoxicity, weight loss**,** and improved β-cell function.
- Data on direct effects on insulin sensitivity remain inconclusive.

Examples

- Empagliflozin, Dapagliflozin, Canagliflozin

Clinical Evidence

- Dapagliflozin improved HOMA-IR in obese and diabetic individuals (Merovci et al., 2014).
- Empagliflozin showed enhanced insulin sensitivity in preclinical and some human studies.

3.3 Tirzepatide (Dual GIP/GLP-1 Receptor Agonist)

Mechanism of Action

Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, leading to a synergistic effect on insulin secretion, satiety, and glucose homeostasis.

Impact on Insulin Resistance

- Significant reductions in HOMA2-IR scores.
- Elevates adiponectin levels, which are inversely related to insulin resistance.
- Combines incretin effects with marked body weight and visceral fat reduction.

Clinical Evidence

- SURPASS trials showed superior glycemic control and HOMA-IR improvement compared to GLP-1 RAs (Frias et al., 2021).
- Outperforms semaglutide in reducing insulin resistance and obesity markers.

3.4 Thiazolidinediones (TZDs)

TZDs activate peroxisome proliferator-activated receptor gamma (PPAR-γ), enhancing insulin sensitivity in adipose tissue, liver, and muscle by modulating gene transcription.

Impact on Insulin Resistance

- Direct and potent insulin sensitizers.
- Improve glucose uptake and reduce hepatic glucose production.

Examples

- Pioglitazone, Rosiglitazone

Clinical Evidence

- Pioglitazone significantly improves insulin resistance in NAFLD and PCOS.
- Long-term use is limited by weight gain, edema, and fracture risk (Nissen & Wolski, 2007).

3.5 Investigational Agents: Azemiglitazone (MSDC-0602K)

Mechanism of Action

- Mitochondrial-targeted PPAR-γ modulator with reduced classical PPAR-γ binding.
- Designed to retain insulin-sensitizing effects without TZD-associated side effects.

Impact on Insulin Resistance

- Early studies show improvement in insulin sensitivity and hepatic lipid metabolism.
- Potential to treat insulin resistance in T2DM and NAFLD without causing weight gain.

Clinical Evidence

- Phase II trials report improved liver enzymes and insulin sensitivity, making it a promising future therapy (Loomba et al., 2021).

Table-01: Comparison Summary Table.

Drug Class	Mechanism	Insulin Resistance Impact	Weight Loss	HOMA-IR Improvement	Other Benefits
GLP-1 RAs	Incretin mimetic	Indirect	Yes	Mild–Moderate	CV benefit, appetite suppression
SGLT-2 Inhibitors	Renal glucose excretion	Indirect	Yes	Mild	CV/renal benefit
Tirzepatide	Dual GIP/GLP-1 agonist	Direct & Indirect	High	Significant (~8%)	Adiponectin, superior glycemic control
TZDs	PPAR-γ activation	Direct	No	Strong	NAFLD benefit, but with side effects
Azemiglitazone	Mitochondrial PPAR-γ modulation	Direct	Neutral	Moderate	Early promise, fewer side effects

4. Comparative Analysis of Newer Antidiabetic Agents on Insulin Resistance

The emerging landscape of type 2 diabetes mellitus (T2DM) therapy includes several novel pharmacological agents that extend beyond glycemic control to address fundamental pathophysiological mechanisms such as insulin resistance. This section presents a comparative evaluation of newer antidiabetic agents, focusing on their mechanistic impact, clinical efficacy, and outcomes on insulin resistance, with insights drawn from randomized controlled trials, real-world studies, and meta-analyses.

4.1 Mechanistic Comparison

Each class of antidiabetic agents employs a distinct mechanism to improve glucose homeostasis and insulin sensitivity:

Table 2: Mechanistic Comparison.

Drug Class	Primary Mechanism	Insulin Sensitization Mechanism
GLP-1 RAs	Incretin mimetics stimulating insulin secretion and satiety	Indirect via weight loss, anti-inflammatory action
SGLT-2 Inhibitors	Promotes urinary glucose excretion by inhibiting renal reabsorption	Indirect via glucotoxicity reduction, weight loss
Tirzepatide	Dual GIP and GLP-1 receptor agonism	Direct (↑ adiponectin) + indirect via significant weight loss
TZDs	PPAR-γ activation	Direct modulation of insulin-responsive genes
Azemiglitazone	Mitochondrial PPAR-γ modulation (non-classical binding)	Direct, with fewer TZD-associated adverse effects

4.2 Comparative Efficacy on Insulin Resistance Metrics

The table-03 summarizes findings from clinical trials regarding the effect of newer antidiabetic drugs on HOMA-IR, QUICKI, and insulin sensitivity indices:

Table-03: Comparative Efficacy on Insulin Resistance Metrics.

Agent	HOMA-IR Reduction	Weight Loss	Adiponectin Effect	Direct Insulin Sensitizer?	Notable Study
Semaglutide	Mild–Moderate	Yes (~5–15%)	Neutral	No	SUSTAIN series
Dapagliflozin	Mild (~10–15%)	Yes (~3–5%)	Neutral	No	DECLARE-TIMI 58
Tirzepatide	Strong (~25–35%)	Yes (~15–22%)	↑↑ (significant)	Yes (dual mechanism)	SURPASS-1 to 5
Pioglitazone	Strong (~30–40%)	No (↑ weight)	↑ (moderate)	Yes	PRO active, ACT NOW
Azemiglitazone	Moderate (~20–30%)	Neutral	↑ (early data)	Yes	EMMINENCE, MSDC-0602K Phase II

4.3 Comparative Safety and Tolerability

Table-04: Comparative Safety and Tolerability.

Drug Class	Common Adverse Effects	Contraindications
GLP-1 RAs	GI symptoms (nausea, vomiting), rare pancreatitis	History of medullary thyroid cancer
SGLT-2 Inhibitors	Genital infections, volume depletion	eGFR < 30 mL/min, DKA risk
Tirzepatide	Nausea, reduced appetite, rare GI side effects	Similar to GLP-1 RAs
TZDs	Weight gain, edema, fracture risk	CHF (NYHA Class III/IV), liver disease
Azemiglitazone	Mild GI, no edema/weight gain reported	Under investigation

4.4 Cardiometabolic and Extra-Glycemic Benefits

Tirzepatide and SGLT-2 inhibitors provide robust cardiometabolic benefits, including reduced visceral adiposity, improved lipid profiles, and favorable blood pressure effects. TZDs, while effective insulin sensitizers, have limitations

due to fluid retention and cardiovascular risk. GLP-1 RAs are effective in reducing major adverse cardiovascular events (MACE) in high-risk populations.

Table-05: Cardiometabolic and Extra-Glycemic Benefits.

Agent	CV Outcome Benefit	NAFLD/NASH Effect	Renal Protection
Semaglutide	Yes (LEADER)	Yes (↓ liver fat)	Modest
Dapagliflozin	Yes (DECLARE-TIMI 58)	Modest	Strong
Tirzepatide	Under evaluation	Yes (↓ ALT, liver fat)	Promising
Pioglitazone	Mixed	Strong	No direct evidence
Azemiglitazone	Early promise	Yes (in trials)	Unknown

4.5 DISCUSSION

The comparative analysis suggests that tirzepatide currently shows the strongest potential for improving insulin resistance, supported by both direct (adiponectin elevation, metabolic remodeling) and indirect (weight reduction, appetite suppression) pathways. TZDs, particularly pioglitazone, remain potent insulin sensitizers but are limited by safety concerns. SGLT-2 inhibitors and GLP-1 RAs offer modest improvements in insulin sensitivity, mostly secondary to weight loss and glucotoxicity reduction.

The investigational agent azemiglitazone represents a promising new direction in insulin sensitization by combining efficacy with a reduced side effect profile—an advancement over traditional TZDs.

The choice of therapy should be individualized based on the patient's comorbidities, risk profile, weight goals, and tolerance to adverse effects.

5. DISCUSSION

The management of insulin resistance, a central pathophysiological component of type 2 diabetes mellitus (T2DM), remains a critical objective in improving metabolic health and preventing long-term complications. The findings from this comparative evaluation of newer antidiabetic agents highlight important distinctions in their mechanisms, efficacy, and clinical outcomes related to insulin sensitivity. The analysis confirms that tirzepatide, a dual GIP/GLP-1 receptor agonist, demonstrates the most significant and measurable improvement in insulin resistance among the newer agents. Its dual incretin mechanism synergistically enhances glucose homeostasis, reduces body weight substantially, and increases adiponectin levels—an adipokine directly linked to enhanced insulin sensitivity. The SURPASS clinical trial series has consistently shown marked improvements in HOMA-IR and other insulin resistance indices, setting tirzepatide apart from traditional GLP-1 RAs and SGLT-2 inhibitors (Frias et al., 2021).

In contrast, GLP-1 receptor agonists such as semaglutide and liraglutide offer modest improvements in insulin sensitivity, primarily through weight reduction, appetite suppression, and anti-inflammatory effects. Their ability to reduce cardiovascular risk and liver fat in non-alcoholic fatty liver disease (NAFLD) patients adds further value, yet their direct impact on insulin signaling remains limited. SGLT-2 inhibitors like dapagliflozin and empagliflozin also improve insulin sensitivity indirectly by reducing glucotoxicity, body weight, and blood pressure. However, studies suggest that while they confer strong cardiovascular and renal protective effects, their influence on insulin resistance is mild to moderate, with inconsistent results across different populations (Merovci et al., 2014). Thiazolidinediones (TZDs) such as pioglitazone remain among the most potent insulin sensitizers due to their direct activation of PPAR-γ, which regulates gene expression in adipocytes, liver, and muscle. However, their clinical utility is constrained by

adverse effects including weight gain, fluid retention, edema, and a potential risk of heart failure. Despite this, they remain effective, especially in patients with NAFLD or polycystic ovary syndrome (PCOS), where insulin resistance is prominent.

Emerging investigational agents like azemiglitazone (MSDC-0602K) represent an innovative evolution of the TZD class. Designed to act via mitochondrial modulation rather than direct PPAR-γ activation, these compounds may preserve insulin sensitization while minimizing side effects traditionally associated with TZDs. Early trials show promise in improving HOMA-IR and liver function, but larger phase III trials are needed to confirm these benefits (Loomba et al., 2021).

From a clinical perspective, this comparative analysis underscores the need for individualized therapy in T2DM management. Patients with predominant insulin resistance, obesity, or fatty liver disease may benefit most from agents like tirzepatide or pioglitazone. On the other hand, those with established cardiovascular or renal disease may be prioritized for GLP-1 RAs or SGLT-2 inhibitors, despite their limited direct effects on insulin resistance. Additionally, combining agents with complementary mechanisms may offer synergistic benefits. For example, tirzepatide plus an SGLT-2 inhibitor could potentially maximize glycemic, weight, and insulin sensitivity improvements while mitigating adverse effects. However, cost, accessibility, long-term safety, and adherence remain practical considerations. This study is limited by variability in available trial data, differing study designs, and a lack of head-to-head comparisons focusing specifically on insulin resistance endpoints. Further biomarker-based trials using standardized insulin sensitivity measures (e.g., HOMA-IR, euglycemic clamps, adiponectin levels) are needed to clarify the magnitude and durability of effects across drug classes.

CONCLUSION

Insulin resistance is a fundamental defect in the pathogenesis of type 2 diabetes mellitus (T2DM), contributing not only to hyperglycemia but also to an increased risk of cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), and other metabolic complications. While traditional therapies have addressed this condition to varying degrees, the emergence of newer antidiabetic agents has opened up novel therapeutic possibilities that extend beyond glycemic control. This comparative study underscores that tirzepatide, with its dual GIP/GLP-1 receptor agonist activity, represents a significant advancement in insulin resistance management. It has demonstrated superior improvements in HOMA-IR and adiponectin levels, along with robust weight reduction, making it a promising candidate for patients with severe insulin resistance and metabolic syndrome. Thiazolidinediones, particularly pioglitazone, remain effective as direct insulin sensitizers through PPAR-γ activation, especially in patients with NAFLD or PCOS. However, their clinical use is restricted by known adverse effects. Azemiglitazone, a next-generation insulin sensitizer under investigation, may offer the benefits of TZDs with a better safety profile, although more data are needed.

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