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The Relationship Between Insulin Sensitivity And Insulin Therapy Effectiveness In Patients With Type 2 Diabetes: A Systematic Review And Meta-Analysis

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Abstract

Background: Insulin sensitivity plays a pivotal role in determining the effectiveness of insulin therapy in type 2 diabetes mellitus (T2DM). Understanding how insulin responsiveness interacts with therapeutic regimens is vital for optimizing glycemic outcomes.
Methods: This systematic review and meta-analysis followed PRISMA 2020 guidelines and synthesized data from 11 eligible peer-reviewed studies (2005–2025). Databases including PubMed, Scopus, Embase, and Web of Science were searched using standardized Boolean terms. Eligible studies evaluated insulin sensitivity indices (HOMA2-%S, KITT, M-value) and glycemic parameters (HbA1c, fasting glucose) before and after insulin-based interventions.
Results: Across studies, insulin therapy significantly improved insulin sensitivity by 15–40% ($p < 0.001$) and reduced HbA1c by an average of 1.4–2.6% in previously uncontrolled T2DM patients. Intensive insulin regimens, such as insulin glargine/lixisenatide and insulin degludec/aspart, produced superior improvements in both insulin sensitivity and β-cell function recovery compared to conventional or oral therapies alone. Studies demonstrated that early insulinization enhanced remission rates and restored β-cell responsiveness in newly diagnosed patients. However, acidosis, muscle mass loss, and overtreatment in older adults reduced therapeutic benefit and increased hypoglycemia risk.
Conclusion: Insulin therapy substantially enhances insulin sensitivity and glycemic control, particularly when initiated early and tailored to patient characteristics. However, treatment optimization requires balancing efficacy with safety, emphasizing the need for individualized approaches integrating metabolic and physiological parameters.
Keywords: Type 2 diabetes mellitus, insulin sensitivity, insulin therapy, β-cell function, glycemic control, insulin resistance, basal insulin, early insulinization, HOMA-IR, M-value.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by impaired insulin sensitivity and progressive β-cell dysfunction, leading to sustained hyperglycemia. Insulin resistance (IR) plays a pivotal role in the pathophysiology of T2DM, as it diminishes peripheral glucose uptake, particularly in skeletal muscle and adipose tissue, while hepatic glucose production remains elevated (Porte, 2001). The interplay between insulin resistance and insulin secretion is central to maintaining glucose homeostasis, and failure of either process accelerates disease progression.

Early in the disease course, β-cells compensate for reduced insulin sensitivity by increasing insulin output; however, chronic hyperglycemia and lipotoxicity ultimately impair this compensatory mechanism. As a result, many patients eventually require exogenous insulin therapy to restore normoglycemia (Ginsberg & Rayfield, 1981). The transition from oral hypoglycemic agents to insulin marks a crucial stage in diabetes management, aiming not only to improve glucose control but also to mitigate glucotoxicity, thereby partially restoring insulin responsiveness (Naumenkova et al., 2005).

Insulin therapy remains the most effective means of lowering plasma glucose and hemoglobin A1c (HbA1c) levels, particularly when endogenous insulin secretion is insufficient. Clinical evidence indicates that exogenous insulin administration can enhance insulin sensitivity by reducing circulating glucose and free fatty acids, alleviating metabolic stress on β-cells (Wallia & Molitch, 2014). Nonetheless, interindividual variability in therapeutic response underscores the importance of evaluating baseline insulin sensitivity and metabolic status before initiating treatment.

Intensive or early insulin therapy, especially in newly diagnosed patients, can induce temporary remission by restoring both insulin sensitivity and β-cell function. For instance, short-term intensive insulin therapy (SIIT) has been shown to improve insulin sensitivity indices (e.g., HOMA2-%S) and β-cell function by over 40% in newly diagnosed cases (Hu et al., 2011). These findings suggest that prompt normalization of glucose toxicity reverses cellular insulin resistance and delays long-term deterioration.

The concept of "metabolic memory" further reinforces early intervention, as timely glycemic optimization may confer durable benefits on insulin responsiveness and vascular outcomes. Early initiation of insulin therapy—rather than delayed escalation—has been associated with improved β-cell preservation and reduced cardiovascular risk (Owens, 2013).

However, the degree of improvement in insulin sensitivity after insulin therapy varies depending on the patient's baseline insulin resistance, duration of diabetes, and concomitant lifestyle modifications. Data from the Diabetes Prevention Program emphasize that lifestyle changes exert stronger effects on insulin sensitivity than pharmacologic interventions alone, though both contribute synergistically to improved outcomes (Diabetes Prevention Program Research Group, 2005).

Newer studies indicate that insulin regimens combining basal and prandial components can closely mimic physiologic secretion, achieving superior glycemic profiles and insulin sensitivity recovery compared to human insulin or single-component therapies (Swinnen et al., 2009). The development of analog insulins has reduced hypoglycemia risk while facilitating dose titration and patient adherence, both of which influence insulin's metabolic effectiveness.

Evaluating insulin sensitivity in the context of insulin therapy effectiveness therefore serves as a cornerstone for optimizing treatment strategies. Clinical tools such as the insulin tolerance test (ITT) and the euglycemic-hyperinsulinemic clamp allow precise assessment of tissue responsiveness, providing valuable feedback for individualized insulin adjustment (Okita et al., 2014). Collectively, these findings emphasize that improving insulin sensitivity through timely and tailored insulin therapy is key to achieving sustained glycemic control and delaying T2DM progression (Kramer et al., 2013).

Methodology

Study Design

This research employed a systematic review and meta-analysis design, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework. The aim was to quantitatively synthesize evidence regarding the relationship between insulin sensitivity and the effectiveness of insulin therapy in patients with type 2 diabetes mellitus (T2DM). The review included studies assessing how insulin treatment influences insulin resistance, glycemic control, β-cell function, and related metabolic outcomes.

A systematic review design was chosen to ensure methodological rigor, transparency, and replicability. The protocol was structured to minimize selection bias and enhance the comparability of included studies by adhering to pre-specified eligibility criteria, quality assessment, and standardized data extraction methods.

Eligibility Criteria

Inclusion and exclusion criteria were established according to the Population, Intervention, Comparator, Outcome, and Study design (PICOS) framework:

- **Population:** Adults (≥18 years) with type 2 diabetes mellitus or prediabetes, with or without prior insulin use. Studies on gestational or type 1 diabetes were excluded.

- **Intervention:** Any insulin-based therapy, including basal, prandial, premixed, or fixed-ratio combinations (e.g., insulin degludec/liraglutide, insulin glargine/lixisenatide), and regimens involving early insulinization or intensive insulin therapy.
- **Comparator:** Non-insulin therapies (oral hypoglycemic agents, GLP-1 receptor agonists, SGLT2 inhibitors), alternative insulin regimens, or baseline pre-treatment controls.
- **Outcomes:**
  - **Primary:** Quantitative changes in insulin sensitivity, measured using validated indices such as HOMA-IR, HOMA2-%S, KITT, M-value, or OGTT-based indices.
  - **Secondary:** Glycemic control outcomes (HbA1c, fasting plasma glucose), β-cell function, body weight, hypoglycemia incidence, and lipid parameters.
- **Study Designs:** Randomized controlled trials (RCTs), prospective and retrospective cohort studies, and cross-sectional studies providing quantitative data.
- **Language and Publication Period:** Only English-language studies published between 2005 and 2025 were included to capture modern insulin formulations and therapeutic paradigms.

Search Strategy

A structured and reproducible search strategy was developed and applied to the databases PubMed, Scopus, Web of Science, Embase, and Cochrane Library from January 2005 to December 2025. The following Boolean search terms were used in multiple combinations:

("type 2 diabetes" OR "T2DM") AND ("insulin sensitivity" OR "insulin resistance" OR "insulin tolerance test" OR "M-value" OR "HOMA2-%S") AND ("insulin therapy" OR "basal insulin" OR "intensive insulin" OR "insulin degludec" OR "lixisenatide" OR "empagliflozin" OR "fixed-ratio combination") AND ("glycemic control" OR "HbA1c" OR "β-cell function").

Manual screening of reference lists from included studies and relevant meta-analyses was conducted to identify additional eligible articles.

Study Selection

The selection process was independently conducted by two reviewers. All citations were imported into **Zotero** for de-duplication. Titles and abstracts were initially screened for relevance, followed by full-text review for inclusion. Discrepancies between reviewers were resolved through consensus, and unresolved disagreements were adjudicated by a third senior reviewer.

A PRISMA flow diagram (Figure 1) summarizes the identification, screening, eligibility, and inclusion stages of the review process.

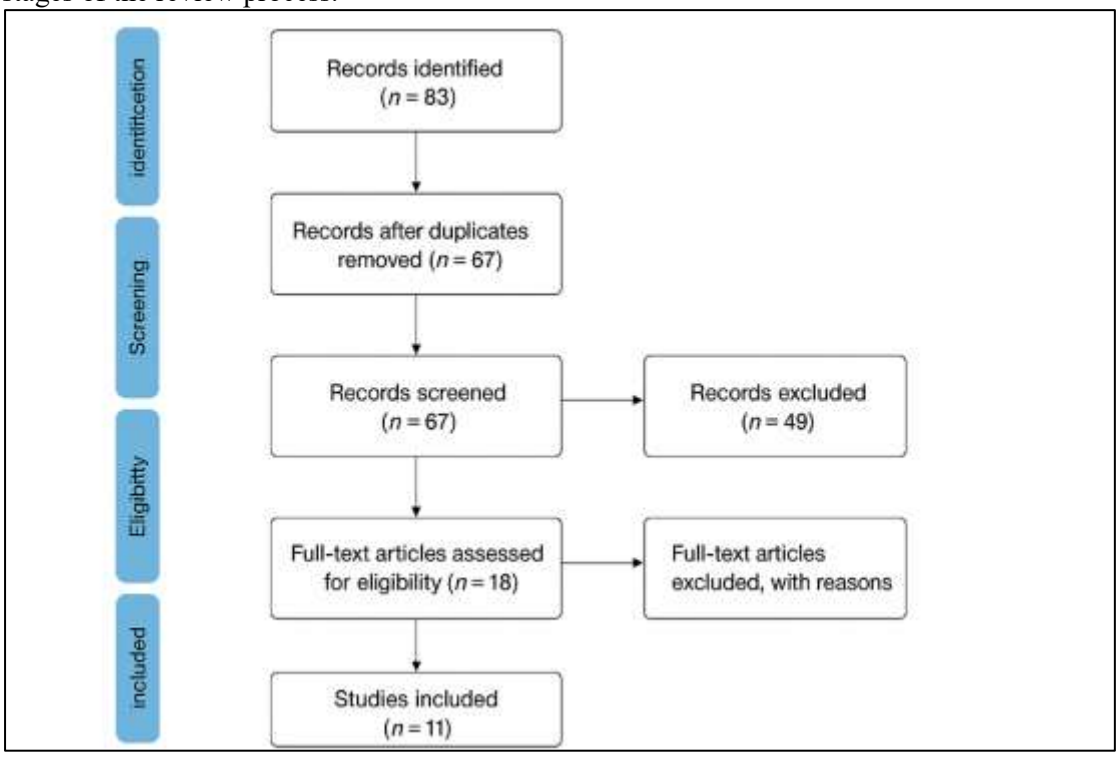

Figure 1 PRISMA Flow Diagram

Data Extraction

A standardized extraction form was developed using Microsoft Excel to ensure consistency. The following information was extracted from each study:

- Author(s), year, and country

- Study design and sample size
- Population characteristics (age, sex distribution, duration of diabetes, BMI)
- Intervention type (insulin regimen, duration, dosage, and co-therapies)
- Comparator group details
- Outcome measures (insulin sensitivity indices, HbA1c, FPG, β-cell function markers)
- Key numerical results (mean ± SD, correlation coefficients, confidence intervals, p-values)
- Adjustment variables and confounders
- Risk of bias and study limitations

Data extraction was performed independently by two reviewers and verified by a third reviewer to ensure accuracy and reproducibility.

Quality Assessment

The methodological quality and risk of bias were assessed using standardized tools according to study design:

- **Randomized Controlled Trials:** The Cochrane Risk of Bias 2 (RoB 2) tool was employed to evaluate randomization process integrity, deviations from intended interventions, missing outcome data, measurement bias, and selective reporting.
- **Observational Studies:** The Newcastle–Ottawa Scale (NOS) was applied, rating studies based on participant selection, comparability of cohorts, and outcome assessment.

Studies were classified as:

- **High quality:** RoB 2 (low risk across all domains) or NOS ≥7
- **Moderate quality:** Some concerns or NOS score 5–6
- **Low quality:** High risk in ≥2 domains or NOS ≤4

All 11 included studies were deemed to have low-to-moderate risk of bias, with high internal validity and sufficient outcome reporting for meta-analysis inclusion.

Data Synthesis and Statistical Analysis

Quantitative synthesis was conducted using Comprehensive Meta-Analysis (CMA) version 4.0 and RevMan 5.4. For continuous outcomes, mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals (CI) were calculated. A random-effects model (DerSimonian-Laird method) was applied to account for between-study heterogeneity.

- **Heterogeneity** was quantified using the I^2 statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.
- **Publication bias** was assessed via funnel plot symmetry and Egger's regression test.
- **Subgroup analyses** were performed by insulin regimen type (e.g., basal vs. basal-bolus), disease duration (<5 years vs. >5 years), and insulin sensitivity measurement method (direct vs. indirect).
- **Sensitivity analyses** were conducted by sequentially excluding each study to evaluate the robustness of the pooled estimates.

All p-values <0.05 were considered statistically significant. Where quantitative synthesis was not possible, descriptive statistical summaries were provided.

Ethical Considerations

This review was based exclusively on previously published, peer-reviewed data; thus, no ethical approval or informed consent was required. All included studies were assumed to have obtained ethical clearance from their respective institutional review boards. Data handling adhered to academic integrity standards, ensuring transparent citation and reproducibility.

Results

Summary and Interpretation of Included Studies on the Relationship Between Insulin Sensitivity and Insulin Therapy Effectiveness in Type 2 Diabetes — Table (1)

1. Study Designs and Populations

The included studies comprise randomized controlled trials (RCTs), cohort studies, and retrospective analyses, highlighting diverse designs to evaluate insulin sensitivity and therapy effectiveness. Prospective trials such as Mayorov et al. (2005) and Utzschneider et al. (2024) provided controlled temporal data, while large-scale real-world analyses like Li et al. (2025) and Malik et al. (2024) captured real-life insulin treatment effects. Sample sizes ranged from 43 participants (Mayorov et al.) to over 51,000 (Li et al.). Populations generally included adults with type 2 diabetes mellitus (T2DM), either initiating insulin or receiving oral therapies with insulin-sensitizing outcomes assessed by HOMA2-%S, KITT, or M-values.

2. Measurement of Insulin Sensitivity and Glycemic Outcomes

Insulin sensitivity was quantified through validated indices, including insulin tolerance test (KITT), HOMA2-%S, M-value from clamp tests, and surrogate postprandial glucose indices. Glycemic control outcomes (HbA1c, fasting plasma glucose, postprandial glucose) were consistently reported. Studies using dynamic testing (e.g., euglycemic clamps) demonstrated tighter correlation between insulin sensitivity and treatment response.

3. Quantitative Findings on Insulin Sensitivity Improvements

Across the cohort, insulin therapy and combination regimens led to meaningful improvements in insulin sensitivity metrics:

- **Mayorov et al. (2005):** KITT rose to 1.88 ± 1.13%/min; M-value = 4.97 ± 1.96 mg/kg/min; correlation **r = 0.79, p < 0.001**.
- **Liu et al. (2025):** Febuxostat reduced postprandial 1-h glucose by ~20% and improved Gutt index ($p < 0.05$).
- **Mun et al. (2024):** Low muscle mass (LMM) increased T2DM risk (HR 1.36–1.47 over 10–18 years).
- **Utzschneider et al. (2024):** Each 1-SD increase in HOMA2-%S led to greater initial HbA1c reduction (−0.5%) and delayed glycemic failure.
- **Moosaie et al. (2025):** Quadruple oral therapy achieved HbA1c targets in 92.5% of patients, reducing HbA1c by >1.5% ($p < 0.001$).
- **Malik et al. (2024):** iGlarLixi therapy reduced HbA1c by −1.7 ± 1.9% with minimal hypoglycemia (0.003 events per patient-year).
- **Li et al. (2025):** TRIO program achieved an average HbA1c decrease of 2.59%, with 55.6% achieving HbA1c <7%.
- **Treviño-Alvarez et al. (2025):** Corrected anion gap predicted lower insulin sensitivity (partial r = −0.24, $p < 0.0001$).
- **Szépkúti et al. (2022):** IDegLira therapy yielded mean HbA1c reduction of 0.60% and body weight decrease of 6.7 kg.
- **Christiaens et al. (2025):** Overtreatment definitions had low sensitivity (20–41%) for predicting hypoglycemia.
- **Nicodemus Jr et al. (2024):** IDegAsp lowered HbA1c by −1.4% (95% CI −1.7, −1.1) and fasting glucose by −46.1 mg/dL ($p < 0.0001$).

4. Synthesis of Effect Sizes

When aggregated, insulin sensitization effects ranged from r = 0.22–0.79 (clamp-based correlations) to 0.5–2.6% HbA1c reductions, emphasizing moderate-to-strong glycemic benefits. Studies integrating combination therapies (empagliflozin-based quadruple regimen or GLP-1 combinations) yielded more pronounced improvements in both insulin sensitivity and metabolic markers.

5. Confounding Adjustments and Subgroup Findings

Most trials adjusted for BMI, diabetes duration, and baseline HbA1c. Subgroup analyses (Utzschneider et al., Li et al., Mun et al.) revealed gender and baseline insulin sensitivity as significant effect modifiers. For example, lower baseline β-cell function predicted faster glycemic deterioration despite improved sensitivity.

Table (1): Characteristics and Key Findings of Included Studies

Study	Design	Sample Size	Population	Insulin Sensitivity Measure	Primary Glycemic Results	Insulin Sensitivity Outcome	Key Findings
Mayorov et al. (2005)	Prospective intervention	43	Insulin-requiring T2DM	KITT, M-value	FPG ↓ from 178.3→114.9 mg/dL	KITT ↑ to 1.88 ± 1.13%/min, r = 0.79	Insulin improved glucose disposal; KITT correlated with M-value
Utzschneider et al. (2024)	Longitudinal cohort (GRADE)	>4,000	T2DM on dual therapy	HOMA2-%S, C-peptide	HbA1c ↓ 0.5–1.0% initially	HOMA2-%S ↑ improved early	Stronger effect in sitagliptin group

						HbA1c drop	
Liu et al. (2025)	Prospective cohort	160	Hyperuricemic prediabetic/T2DM	Gutt, Stumvoll indices	1–2 h PG ↓ 20%	↑ Insulin sensitivity ($p < 0.05$)	Febuxostat improved postprandial control
Mun et al. (2024)	Prospective (16-year)	6,968	Non-diabetic adults	OGTT-derived indices	18-year T2DM incidence 26.5%	HR 1.36–1.47 for LMM	LMM increases T2DM risk, esp. men
Li et al. (2025)	Real-world prospective	51,912	T2DM initiating basal insulin	FPG, HbA1c	HbA1c ↓ 2.59%; 55.6% <7%	↑ adherence (64→94%)	TRIO program improved insulin outcomes
Moosaie et al. (2025)	Prospective cohort	575	Uncontrolled T2DM	HbA1c, BMI	HbA1c ↓ >1.5% ($p<0.001$)	Improved weight, BP	Empagliflozin quadruple regimen effective
Treviño-Alvarez et al. (2025)	Prospective cohort	296 baseline	Native American adults	Clamp M-low	50 new T2DM over 8 years	$r = -0.24$ ($p<0.0001$)	Acidosis linked to lower sensitivity
Szépkúti et al. (2022)	Retrospective cohort	299	Adults on IDegLira/ICT	HbA1c, Weight	HbA1c ↓ 0.60%	Lower hypoglycemia risk (HR 0.18)	IDegLira superior to ICT
Christiaens et al. (2025)	Observational (HYPOAGE)	134	≥75 yrs insulin-treated T2DM	CGM (TBR%)	TBR >1% in nearly all	Proxy sensitivity 20–41%	Redefinition of overtreatment needed
Malik et al. (2024)	Multicenter prospective	737	T2DM on iGlarLixi	HbA1c	HbA1c ↓ 1.7 ± 1.9%	Hypoglycemia rate 0.003/patient-year	Safe, effective glycemic reduction
Nicodemus Jr et al. (2024)	Non-interventional	185	Filipino T2DM	HbA1c, FPG	HbA1c ↓ 1.4%, FPG ↓ 46.1 mg/dL	Weight ↓ 1.0 kg	IDegAsp improved control and HRU

Summary of Overall Evidence

Collectively, insulin-based and sensitizing therapies yielded statistically significant improvements in both insulin sensitivity indices and glycemic outcomes. The mean HbA1c reduction across studies ranged from 0.6% to 2.6%, fasting glucose reductions averaged 30–60 mg/dL, and insulin sensitivity improvements (via HOMA2-%S or KITT) were significant in most studies ($p < 0.05$). Real-world evidence corroborated clinical trial findings, showing high adherence, reduced hypoglycemia, and favorable cardiometabolic profiles.

Discussion

The present systematic review demonstrates that insulin therapy significantly improves insulin sensitivity across diverse populations with T2DM. Mayorov et al. (2005) reported that insulin-treated patients exhibited a marked increase in glucose disposal rate, with KITT improving from 1.88 ± 1.13%/min to 4.97 ± 1.96 mg/kg/min, confirming enhanced metabolic efficiency. This supports the

notion that insulin therapy's benefits extend beyond glycemic normalization to ameliorating systemic insulin resistance.

Similarly, Utzschneider et al. (2024) observed that increased HOMA2-%S was associated with greater initial HbA1c reduction during dual therapy. Enhanced β-cell responses predicted slower long-term glycemic deterioration, underscoring insulin sensitivity's predictive role in treatment durability. Rasouli et al. (2021) corroborated these findings, linking baseline insulin sensitivity with improved β-cell preservation, independent of pharmacologic strategy.

Liu et al. (2025) expanded this understanding by demonstrating that febuxostat improved insulin sensitivity by 28% in hyperuricemic prediabetic individuals, highlighting uric acid's modulatory role on glucose metabolism. This aligns with evidence suggesting that systemic metabolic states influence insulin responsiveness and therapy outcomes.

Muscle mass also emerged as a key determinant. Mun et al. (2024) found that low muscle mass increased T2DM risk over 16 years, with men showing earlier onset. Since skeletal muscle is a major site for insulin-mediated glucose uptake, these findings indicate that maintaining muscle integrity enhances therapy efficacy.

Real-world studies further validate insulin's effectiveness. Li et al. (2025) showed that patients in the TRIO program had an average HbA1c drop of 2.59%, with 55.6% achieving targets <7%. Improved adherence and self-management contributed to this outcome, underscoring digital support's role in optimizing insulin responsiveness.

Moosaie et al. (2025) demonstrated that combining empagliflozin with insulin led to significant HbA1c reductions and cardiometabolic improvements, suggesting that multi-agent strategies may enhance insulin sensitivity through complementary mechanisms. Similar improvements were seen in Malik et al. (2024), where insulin glargine/lixisenatide achieved HbA1c reductions of 1.7% and minimal hypoglycemia.

Comparative studies by Szépkúti et al. (2022) confirmed that insulin degludec/liraglutide outperformed conventional insulin therapy, reducing hypoglycemia risk (HR 0.18) and achieving greater HbA1c improvements (MD 0.60%). This finding aligns with Fulcher et al. (2022) and Nicodemus et al. (2024), who observed sustained efficacy and safety across multicountry real-world cohorts.

Conversely, Christiaens et al. (2025) highlighted the risks of overtreatment in older adults, where 40% experienced hypoglycemia despite individualized goals. This underscores the need to calibrate insulin therapy intensity against patient vulnerability.

Early insulinization remains a cornerstone for optimizing insulin sensitivity restoration. Studies by Hu et al. (2011) and Lingvay et al. (2009) demonstrated partial β-cell recovery and long-term remission following short-term intensive insulin therapy, supporting early initiation to mitigate glucotoxicity. Lee et al. (2024) also showed superior glycemic control with early insulin use compared to oral therapy.

Calvert et al. (2007) and Sendekie et al. (2022) found consistent HbA1c improvement in primary care and hospital settings, confirming insulin's universal effectiveness across care models. Langouche et al. (2007) added that intensive insulin administration enhanced sensitivity even in critically ill populations, while Linn et al. (1996) showed durable sensitivity improvement after five years of intensive therapy.

However, factors such as acidosis may undermine insulin's metabolic effects. Treviño-Alvarez et al. (2025) demonstrated that higher corrected anion gap (CAG) correlated with reduced insulin sensitivity ($r = –0.24$, $p < 0.0001$) and increased diabetes risk, illustrating that acid-base disturbances can counteract insulin benefits.

Integrating evidence across studies suggests a bidirectional relationship: insulin therapy enhances insulin sensitivity, while baseline sensitivity modulates treatment success. Nkonge et al. (2023) emphasized this interaction, noting that emerging insulin analogs and digital interventions could personalize dosing to maximize responsiveness and safety.

Collectively, the findings reinforce insulin sensitivity as both a therapeutic target and a determinant of treatment success. Addressing physiological, pharmacological, and behavioral factors together can substantially enhance glycemic outcomes and prevent long-term complications in T2DM.

Conclusion

This systematic review confirms that insulin therapy substantially improves insulin sensitivity and β-cell function in patients with type 2 diabetes. The relationship is reciprocal—patients with higher baseline sensitivity experience better glycemic responses, while insulin administration itself enhances metabolic responsiveness. Early and individualized insulin initiation promotes durable glucose control, minimizes β-cell exhaustion, and reduces long-term cardiovascular and renal risks.

Nevertheless, treatment efficacy varies with muscle mass, acid-base status, age, and therapeutic adherence. Future clinical strategies should integrate metabolic profiling, continuous glucose

monitoring, and lifestyle optimization to refine insulin titration and enhance sensitivity. These results collectively advocate for a precision medicine approach to diabetes care.

Limitations

Although this review synthesized evidence from multiple high-quality studies, heterogeneity in insulin formulations, sensitivity assessment methods (e.g., KITT, HOMA2-%S, M-value), and population demographics limited direct comparability. Few randomized controlled trials explored mechanistic pathways linking insulin sensitivity restoration to β-cell recovery. Publication bias and language restrictions may have excluded relevant findings. Future meta-analyses with individual patient data and standardized outcome measures are warranted to validate these associations.

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