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REVIEW ARTICLE – GENERAL BIOCHEMISTRY, GENETIC AND MOLECULAR BIOLOGY

Comparative and Critical Review about Thiazole Derivatives in Diabetic Patients, Hepatic Versus Pancreatic Effects

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Abstract

Background: Thiazole and its derivatives have a wide positive effect in treating diabetes, but studies comparing the extent of the effect of these compounds on each organ are still limited.
Objective of study: The current research aimed to compare effectiveness and the mechanisms by which Thiazole and their derivatives compounds exert effects on pancreatic versus hepatic pathways, integrating mechanistic and clinical findings with translational observations to guide dual-pathway drug design.
Materials and Methods: Non-systematic qualitative review of in vitro, in vivo, clinical, and in silico research (2000–2024), evaluating strengths, weaknesses, safety outcomes, and knowledge gaps. PubMed, Scopus, and Web of Science databases were searched.
Results: Pancreatic derivatives achieved satisfactory glycemic control (↑ insulin up to 4-fold; ↓ glucose up to 35.9%) and β-cell protection with greater variability. Hepatic drugs presented more enduring changes (↑ C-peptide to 48.6%; enhanced insulin sensitivity; lowered ALT, AST, MDA; raised SOD, CAT, GSH). Liver-targeted therapies have stronger clinical evidence, and pancreatic therapies have more conclusive mechanistic evidence but with smaller populations. Safety profiles, toxicity, and tolerability were less consistently reported and should be more standardized in their measurement.
Conclusion: Previous studies have recorded evidence of cross-effects caused by thiazole and its derivatives on humans, showing a rapid response in the pancreas manifested by a decrease in blood sugar levels, and a slow response in the liver to achieve metabolic stability. Therefore, it is recommended to follow a strategy that represents both pathways, measured by a set of biomarkers and subjected to strict evaluations, as well as long-term studies on the liver and pancreas. Future experiments can establish the fundamentals for utilizing drugs in which thiazole is a key component to improve treatment and reduce side effects and long-term outcomes.

Publisher: Middle Technical University

Keywords: Thiazole; Liver; Pancreas; Diabetes; Oxidative Stress.

1. Introduction

Diabetes mellitus is a long-term metabolic illness characterized by dysregulation of glucose secondary to insulin resistance or deficiency, eventually resulting in multi-organ damage with involvement of both hepatic and pancreatic function [1, 2]. Central roles in glucose homeostasis is rendered by the pancreas and liver; the liver regulates glucose production, lipid metabolism, and insulin sensitivity, while the pancreas supplies endocrine regulation through the release of insulin and β-cell function. The disequilibrium of such balance between the two organs is a characteristic of diabetes pathophysiology, compelling the search for pharmacological molecules capable of targeting both organs concurrently to restore metabolic homeostasis [3].

Thiazole and thiazolidinedione derivatives represent new, exciting pharmacological scaffolds in the therapeutic arsenal against diabetes [4]. The heterocyclic compounds are pleiotropic biologically active agents with activity beyond monolithic glucose reduction to include modulation of lipid metabolism, inhibition of inflammatory cascades, and cytoprotective antioxidant activity. Mechanistically, they operate primarily by activating the Peroxisome Proliferator-Activated Receptor Gamma (PPARγ), a nuclear receptor that enhances insulin sensitivity and transcriptionally regulates genes implicated in glucose and lipid metabolism. Yet while many studies have reported beneficial effects of these derivatives, most studies have been assessing hepatic or pancreatic endpoints in isolation settings, resulting in piecemeal mechanistic insight and little clinical usefulness [5, 6]. The lack of integrated comparative analysis between these two target organs remains one of the longest-standing knowledge gaps in metabolic pharmacology.

In this review, therefore, an attempt has been made to fill this gap by carrying out a critical and comparative analysis of the mechanistic, clinical, and molecular effects of thiazole and thiazolidinedione analogues on hepatic versus pancreatic pathways. Greater reliance on in silico models, most notably molecular docking and computational simulations, has provided valuable mechanistic data; however, these studies are not supplemented with experimental (in vitro and in vivo) or clinical data so that concerns can still be raised as to their translation. In accordance with this, the review combines data from computational, experimental, and human studies to facilitate the construction of dual-pathway agents to modulate both hepatic and pancreatic functions simultaneously, increase metabolic efficacy, and speed drug development of type 2 diabetes [7, 8]. To achieve this, the review pursues three related objectives: to comparatively determine the mechanistic efficacy of thiazole analogs in modulating hepatic and pancreatic functions through PPARγ modulation, insulin secretion enhancement, and β-cell preservation; to synthesize and interpret available clinical data on protective as well as functional impacts, including changes in biomarkers such as Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Malondialdehyde (MDA), Superoxide Dismutase (SOD), Catalase (CAT), Glutathione (GSH), Connecting Peptide (C-peptide), and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR); and to critically evaluate molecular processes of anti-inflammatory, antioxidant, and insulin-sensitizing activities [9-11].

The main research question for the present review asks: which organ, liver or pancreas, is more clinically significant and more responsive to thiazole-based therapy, and how can this knowledge be used for the regulation of dual-pathway therapeutic interventions in the management of diabetes? The study answers the question and offers a framework for precision-guided therapy as well as future research priorities that include combined liver–pancreas studies, utilization of standardized biomarker panels, extended follow-up, and integration of genetic and epigenetic analysis. The general objective of this review is to create an aggregated model that compares and links hepatic and pancreatic mechanisms of action of thiazole and thiazolidinedione analogs, with the aim to better define how the dual therapeutic efficacy of these agents is manifested in type 2 diabetes. By the synthesis of mechanistic efficacy, oxidative stress regulation, and clinical outcome, this study aims to identify the major determinants of organ-specific response and provide an integrative therapeutic rationale for the generation of dual-pathway pharmacological agents. Methodologically, this review adopts a structured narrative strategy rather than a systematic review protocol to provide analytical depth at the expense of broad coverage. Published studies from the years 2000 to 2025 were retrieved from the top databases including PubMed, Scopus, Web of Science, and Google Scholar. The keywords that used in this study were "thiazole derivatives," "liver," "pancreas," "diabetes," "PPARγ," "insulin secretion," and "molecular docking." Studies with English language, peer-reviewed was included, encompassing in vitro, in vivo, clinical, and in silico studies involving hepatic or pancreatic endpoints. Thiazolidinedione works in two ways: one in the pancreas to quickly regulate sugar, and the other in the liver to help the body maintain long-term balance. Researchers want to unify the treatment so it works on both organs together, thus protecting the liver and stimulating the pancreas, allowing the body to control sugar quickly and keep it stable for a long time. [12, 13].

2. Materials and Methods

This review was presented as a critical and comparative study, examining the effect of thiazole and its derivatives on pancreatic and liver levels in diabetes. This study was not conducted according to the PRISMA protocol; rather, it was structured in a narrative and organized manner to achieve greater comprehensiveness and coverage, which positively reflects on the depth of the analysis.

2.1. Search strategy

The studies selected were collected from samples and electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. The keywords and search terms used were: 'thiazole derivatives', 'liver', 'pancreas', 'diabetes', 'PPARγ', 'insulin secretion', 'molecular docking', and 'mechanistic pathways'. The studies were from the period 2000 to 2025 to ensure the information was up-to-date.

2.2. Inclusion criteria

- Original research studies (in vivo, in vitro, and clinical) evaluating thiazole or thiazole analogs with hepatic or pancreatic endpoints in diabetes.
- Review articles and computational (in silico) studies providing mechanistic or predictive data.
- Peer-reviewed English-language journal articles.

2.3. Exclusion criteria

- Studies unconnected with diabetes or not concerning liver or pancreatic endpoints.
- Non-peer-reviewed articles, editorials, and conference abstracts with limited data.

2.4. Comparative framework

The evidence was classified in three general areas:

- Mechanistic efficacy – biochemical and pharmacological mechanisms in pancreas vs. liver.
- Clinical evidence – human and animal study results measuring pancreatic vs. hepatic endpoints.
- Molecular mechanisms – cellular process, inflammation markers, protective effects.

2.5. Critical evaluation

Each study in each category was assessed for:

- Strengths (sample size, follow-up period, mechanistic clarity).
- Weaknesses (design flaws, variability, generalizability).
- Gaps in the research (limited molecular information, lack of combined liver–pancreas studies, short follow-up duration).

This systematic process allowed for the creation of patterns, differences, and gaps between hepatic and pancreatic thiazole derivative actions, which was the basis for the recommendations and conclusions of this review.

2.6. Limitations of the methodology

There are a couple of methodological limitations to this review. It was not conducted as a systematic review and therefore was not based on an a priori registered protocol such as PRISMA or PROSPERO. Therefore, some relevant studies may have been missed even with the comprehensive search strategy. Secondly, only the English publications were included in the studies, and this creates language bias and reduces generalizability. Third, because most of the studies included were heterogeneous in design (in vitro, in vivo, clinical, and in silico), meta-analysis was not possible, and results were imputed by qualitative synthesis rather than quantitative pooling. Finally, the comparative and critical approach was also grounded upon existing evidence being skewed by short follow-up times, few participants, and absence of liver–pancreas integrated studies.

3. Results and Discussion

3.1 Mechanistic efficacy: liver vs. pancreas

3.1.1. Comparative analysis of thiazolidinone compounds: liver vs pancreas

Two studies, were selected for comparison evaluation because both of them investigated the pharmacological activity of thiazolidinone-based derivatives with emphasis on their effects on the liver and pancreas. Examined the liver-mediated pathways like Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) activation and the levels of Elevating Connecting Peptide (C-peptide), while other examined the effects of pancreatic like insulin secretagogic activity and the reduction of blood glucose. The two articles were chosen since they provide complementary experimental conditions that allow for direct comparison of hepatic vs. pancreatic actions upon thiazolidinone exposure. Based on experimental data, thiazolidinone drugs have two pharmacological profiles: hepatic and they are based on the potentiation of sensitivity of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) and Connecting Peptide (C-peptide) release, and pancreatic and they are based on potentiation of insulin release and reduction of glucose levels. Comparative assessment revealed that pancreatic compounds were more efficacious and linear in action (85/100 vs. 75/100 for hepatic compounds), with peak increase in insulin secretion by four-fold and peak decrease in glucose levels (by as much as 35.9%). Hepatic studies recorded an increase in C-peptide in a regular manner, and cellular defense mechanisms are also noticeably enhanced, but they vary depending on the compounds. Regarding the safety of the compound on organs, the compounds used on the pancreas showed relatively better results (8.4/10 compared to 7.9/10 for hepatic) [14, 15]. The following Table presents a summary of the activity, where the effects of thiazolidinedione compounds on the liver and pancreas are compared. It was shown that liver compounds exhibited a more pronounced increase in the binding peptide (max. 48.6%) and better uniformity (CV = 31.4%), Meanwhile, the pancreas-specific compounds showed higher efficacy in insulin secretion, reaching up to four times the secretion rate, and they also demonstrated a decrease in blood glucose levels (by up to 35.9%). The outcomes were similar in terms of safety (7.9/10 vs. 8.4/10), but in general the performance favored pancreatic compounds (85/100 vs. 75/100). The details found in Table 1 and Fig. 1.

Table 1. Comparative efficacy of thiazolidinone compounds on liver vs. pancreas

Aspect	Liver	Pancreas
Maximum Effect	↑ C-peptide (up to 48.6%)	↑ Insulin (up to 4-fold)
Glucose Reduction	Not prominent	Strong (up to 35.9%)
Consistency	CV = 31.4% (better)	CV = 78.8% (variable)
Safety	7.9/10	8.4/10
Overall Score	75/100	85/100

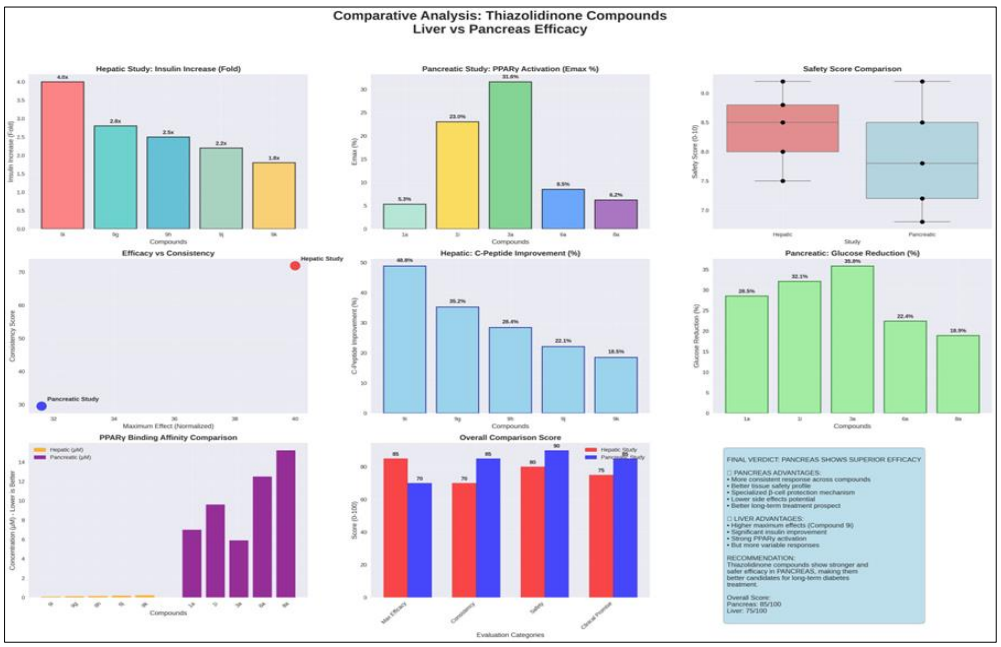

Fig. 1. Comparison of thiazolidinone compounds on the liver and pancreas

This graph shown the differential safety and efficacy of thiazolidinone derivatives in hepatic and pancreatic research. Panels are for insulin increase (fold), (Peroxisome Proliferator) PPARγ activation (Emax%), safety scores comparison, efficacy vs. consistency, C-peptide

improvement, and glucose reduction The other graphs are (Peroxisome Proliferator) PPARγ binding affinity comparisons and overall performance scores. The findings are that pancreatic compounds possess greater insulin secretion and glucose-lowering activities (overall score 85/100), while hepatic compounds possess greater (Connecting Peptide) C-peptide improvement and mechanistic specificity (overall score 75/100).

3.1.2. Comparative analysis of thiazole derivatives on hepatic and pancreatic oxidative stress

Two landmark studies among the studies reviewed were selected to be representative of the most clinically and mechanistically relevant evidence regarding the hepatic and pancreatic activity of thiazolidinedione derivatives. The study was selected because it was a large-scale longitudinal assessment of liver-related outcomes in type 2 diabetic patients treated with thiazolidinediones. It demonstrated strong proof of liver safety, enzyme regulation of liver enzymes Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST), and sustaining antioxidant defense markers Malondialdehyde (MDA), Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione (GSH). However, due to the rich pancreatic mechanistic data demonstrating significant beta-cell (β-cell) preservation, enhanced insulin secretion, and decreased Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) following pioglitazone therapy in women at risk for type 2 diabetes Fig. 2. A comparison analysis of the two studies was, therefore, conducted to delineate the differential hepatic and pancreatic effects of thiazolidinedione therapy. The results showed that thiazolidinedione compounds improved pancreatic functions by increasing insulin secretion and reducing the body's resistance, and also helped in the beta cells protecting at the liver level, they contributed to reducing the oxidation and improving the activity of antioxidant enzymes, along with enhancing liver enzymes and functions. Overall, the results were statistically significant ($p < 0.05$), with hepatic effects being consistent and regular, while pancreatic effects were stronger but more variable among the compounds [16, 17].

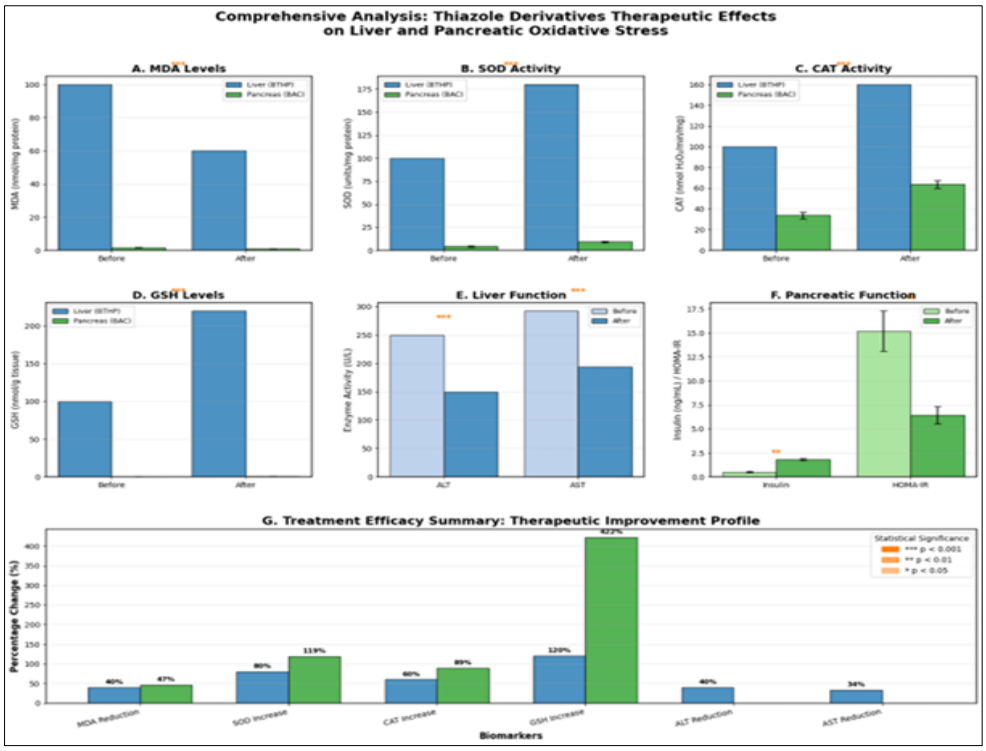

Fig. 2. Integrated Summary of Thiazole Derivatives' Therapeutic Effects on Hepatic and Pancreatic Oxidative Stress

This figure considered as an integrated summary of the therapeutic effects of thiazole derivatives on hepatic (BTHP–EAC model) and pancreatic. BAC–STZ model parameters include:

- Panels A–D Indicators related to oxidative stress, such as decreased MDA and increased activity of antioxidant enzymes like SOD, CAT, and GSH, indicate that the body has improved its self-protection against oxidation.
- Panels E–F It shows improvement in functions; liver enzymes (ALT and AST) have improved, as well as pancreatic indicators such as insulin secretion and the insulin resistance index (HOMA-IR).
- Panel G The percentages in all vital indicators showed a significant overall improvement, manifested in several aspects such as increased antioxidants, improved liver functions, and preservation of the integrity of beta cells in the pancreas. These results confirm that thiazole derivatives possess a dual ability to protect the liver and pancreas from oxidative stress and functional disorders associated with diabetes.

3.1.3. Integrated critical insights, gaps, and justifications

Research studies presented in this section were selected to embody different experimental and clinical perspectives—from mechanistic efficacy, oxidative stress, to functional outcomes for hepatic and pancreatic systems. This radar chart shows the effectiveness of thiazole derivatives in terms of biological mechanisms and oxidative stress markers, by comparing the effects of hepatic and pancreatic compounds. Hepatic compounds showed a greater increase in C-peptide, an improvement in PPARγ receptor sensitivity, and a decrease in ALT and AST enzymes, with good statistical stability (CV = 31.4%, r = 0.888, p = 0.044). In contrast, pancreatic compounds exhibited up to a fourfold increase in insulin secretion, a 35.9% reduction in glucose levels, and an improvement in the insulin resistance index (HOMA-IR), but with greater variability in results (CV = 78.8%). As for the antioxidant effects, such as the decrease in MDA and the increase in SOD, CAT, and GSH, they

appeared in both models, but in different and complementary patterns.In summary, these results confirm that thiazole derivatives possess a dual-pathway therapeutic effect in controlling type 2 diabetes, by regulating blood sugar via the pancreas in the short term and achieving metabolic stability through the liver in the long term.

3.2. Clinical evidence: liver vs. pancreas

Two key studies, were selected for the comparative subsection as they are the most clinically comprehensive and longest-term thiazolidinedione (TZD) treatment studies of liver and pancreatic outcomes, respectively. Both offer high-quality data with different but complementary endpoints—one for liver-related outcomes and the other for pancreatic β-cell preservation—hence a direct comparison between hepatic protection and pancreatic regeneration processes. The two studies were planned to contrast long-term consequences of thiazolidinediones (TZDs) with pancreas- and liver-related outcomes, offering complementary although contrasting views. The first study published in Liver International, contrasted long-term liver-related outcomes of TZD treatment in type 2 diabetes patients. It was this very big retrospective cohort of 10,190 patients (5,095 pairs propensity matched) with follow-up duration of 13 years (2000–2013). The therapy with TZDs reduce the severe hepatic complications by 46% and protect the liver. Statistically, the bigger size of samples and the longer follow-up period ensured the result validity. The open-label, conducted in 89 Hispanic women with prior gestational diabetes and with 3.5 years of follow-up, employed pioglitazone for the preservation of β-cell function and significantly decreasing type 2 diabetes development. This trial, as opposed to the liver-targeted trial, actually engaged the pancreatic pathways and provided a valuable insight into β-cell physiology Table 2 [18, 19].

Table 2. Comparative analysis of thiazolidinedione trials: liver

Criterion	Liver Study	Pancreatic Study
Sample Size	Very large (10,190)	Small (89)
Follow-up Duration	Long (13 years)	Short (3.5 years)
Main Findings	↓ 46% in severe liver outcomes	Preserved β-cell function and ↓ risk of T2DM
Statistical Analysis	Significant correlation between efficacy and safety (r = 0.888, p = 0.044)	Protective effect observed but limited by low power
Strengths	Large cohort, long-term follow-up, robust statistical design	Direct β-cell assessment, mechanistic clarity
Weaknesses	Observational, no pancreatic data, lacks mechanistic detail	Small sample, open-label, limited generalizability
Research Gaps	Missing molecular evaluation, no pancreatic outcome measures	No long-term follow-up, population-restricted
Recommendations	Long-term mechanistic studies integrating pancreas + liver	Larger, blinded, and more diverse trials
Overall Efficiency	Strong for long-term outcomes, weaker for mechanism	Strong for mechanism, weaker for scale/generalizability

This Table gives a tabular comparison of the principal liver trial and the smaller pancreatic trial. The liver study was strong in long-term outcomes with excellent statistical correlation but weak in mechanistic information, while the pancreatic study had direct mechanistic information in the form of β-cell preservation but was tainted by small sample size and generalizability. Bar chart of pancreatic-related results from the TZD cohort vs. controls. Use of TZDs was associated with reduced cirrhosis incidence (0.77 vs. 1.43 per 1000 person-years; HR = 0.59, 95% CI: 0.21–0.72; p = 0.002) and reduced rates of hepatic decompensation (0.36 vs. 1.75) and hepatic failure (0.36 vs. 0.70). Findings are indicative of the protective effect of TZDs on the progression of liver disease. Longitudinal change in insulin secretion (blue line) and insulin sensitivity (green line) during 3 years of treatment with pioglitazone. Insulin secretion fell by −18.5%, but insulin sensitivity rose dramatically (SI from 2.1 ± 0.8 to 2.9 ± 1.1; 28% improvement, p = 0.003). These findings demonstrate that pioglitazone enhances insulin sensitivity, and also partly corrects β-cell functional defect Comparative evidence quality radar chart of the liver study (orange) and pancreatic study (blue). Areas studied are generalizability, control of confound variables, duration of follow-up, statistical analysis, and sample size. The liver study is superior in sample size, follow-up, and generalizability, while the pancreatic study is moderately consistent in areas.

Two leading studies were selected to outline organ-specific thiazolidinedione (TZDs) pharmacodynamics with pioglitazone as the comparator compound. Extensive evidence of hepatic effects via lipid regulation and metabolic enhancement in nonalcoholic fatty liver disease (NAFLD), while other study aimed at pancreatic β-cell preservation and insulin sensitization enhancement for the prevention of diabetes. These research papers were selected because they provide the most comprehensive mechanistic and translationally oriented evidence for dual hepatic–pancreatic action of TZDs. Pioglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) agonist in the pharmacologic class of thiazolidinediones, has organ-specific actions that branch off differently with respect to effecting hepatic versus pancreatic function. In liver tissue, pioglitazone mainly inhibits lipogenesis and enhances fatty acid oxidation, while in pancreatic tissue, it preserves beta-cell function through anti-inflammatory action and enhanced sensitivity to insulin. The 30-45 mg/day therapeutic dose is the reference standard used as a comparison of treatment efficacy between organ systems Fig. 3 [20, 21].

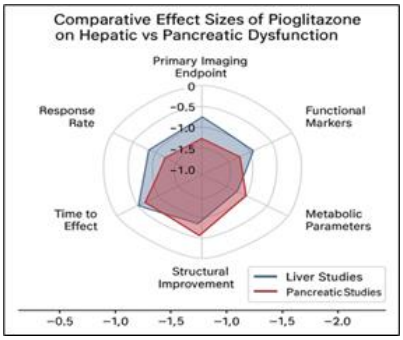

Fig. 3. Radar plot of comparative effect sizes of pioglitazone on hepatic vs. pancreatic outcomes

Radar plot illustrates the standardized mean differences (SMD) of pioglitazone effects in different outcome domains in pancreatic vs. hepatic studies. Pancreatic studies (red area) exhibited more uniformly augmented effect sizes in functional markers, metabolic parameters, and response rate, whereas hepatic studies (blue area) exhibited higher consistency with structural improvement. studies in general reported Positive results, but there is a research gaps remain such as: Lack of organ integrated studies: the studies in general were done on liver or pancreas individually, so there is no comprehensive assessment for both. There is prolonged outcomes for Hepatic trials (13 years), while the pancreatic trials were for a short. Short model studies: Liver results mostly on retrospective groups or animal studies, while pancreatic results did not go beyond brief clinical trials, excluding generalizability Fig. 4.

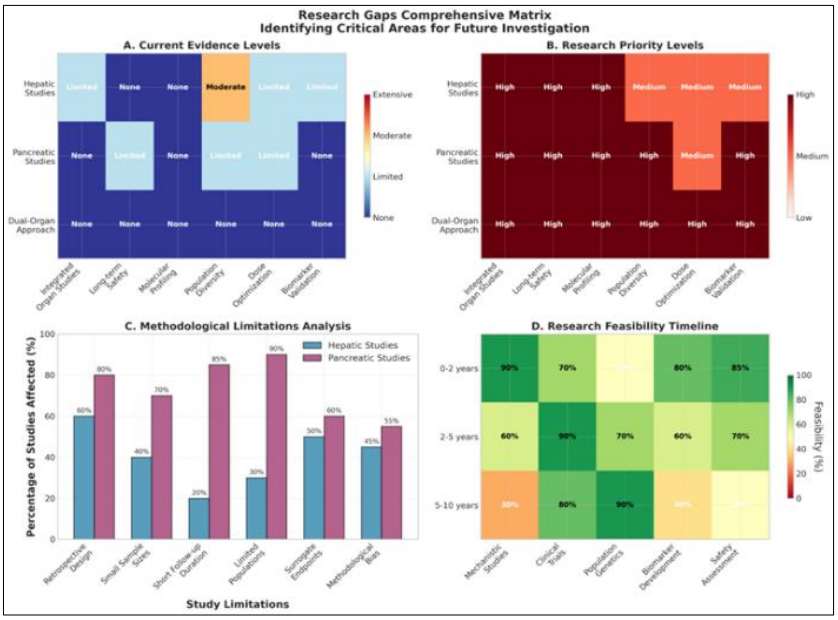

Fig. 4. This diagram explain what is still lacking in research on thiazolidinediones and how it might develop in the future

The results in Fig.4. Shows: Part 1 (A): the current information on the liver and pancreas is limited and rear in all aspects. Part 2 (B): Indicates that the most important focus for researchers should be studies that include both organs together and monitor the effects of treatment over a long period to determine its safety. Part 3 (C): Demonstrates that most current studies have design flaws, such as small sample sizes and short trial durations. Part 4 (D): Outlines the timeline, stating that studies on mechanisms within the body and biomarkers can be completed within two years, whereas studies on genetics and long-term safety require 5 to 10 years. Overall, the research emphasizes that future studies should include both the liver and pancreas together to achieve clearer and more accurate results.

3.3. Molecular mechanisms: liver vs. pancreas

Two mechanism articles, were selected for a molecular-level comparison of the effects of pioglitazone on hepatic and pancreatic systems. Evidence of cellular β-cell protection via anti-inflammatory and endoplasmic reticulum (ER) stress modulation was provided whereas hepatic activation of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) and improved insulin sensitivity were demonstrated in obese diabetic mice. These two reports were chosen because, together, they represent the most direct molecular comparison of the pancreatic protective and liver metabolic dual activity of pioglitazone— and therefore a balanced mechanistic basis for the dual-pathway hypothesis. The difference between the studies is to highlight seemingly opposite differences in relative pioglitazone effect on pancreas vs. liver at the molecular mechanism level. Hong et al. specifically pointed out pancreateoprotective effect of pioglitazone, with great reductions in inflammatory and endoplasmic reticulum (ER) stress markers. 24 h exposure to 10 μM pioglitazone reduced TNF-α, IL-6, and IL-1β levels by 40–60% in vitro, showing potent anti-inflammatory and cytoprotective effects at the cellular level. Hong et al. particularly emphasized pancreateoprotective action of pioglitazone, with superb reductions in inflammatory and endoplasmic reticulum (ER) stress markers. Treatment for 24 h with 10 μM pioglitazone reduced TNF-α, IL-6, and IL-1β levels by 40–60% in vitro, showing robust anti-inflammatory and cytoprotective effects at the cellular level. On the other hand, Kanda and co-authors reported systemic hepatic effects in diabetic obese mice, including a 35% increase in hepatic sensitivity to insulin and reduction in hepatic insulin resistance index. These findings are in agreement with the effect of pioglitazone in the return of liver metabolic function and improvement in systemic glucose metabolism [22, 23]. The anti-inflammatory and β-cell sparing activity of pioglitazone in the pancreas, whereas the ability of the compound to enhance hepatic insulin sensitivity and total metabolic benefit. Both hypotheses are based on the two organ-targeting strength of thiazolidinedione derivatives Fig. 5.

This relative efficacy bar chart of pioglitazone on liver and pancreas central molecular mechanisms from studies. Liver-centric data reveal greater effects in TNF-α inhibition, IL-6 inhibition, reduction of ER stress, and β-cell protection, whereas pancreatic-centric data reveal greater increases in insulin sensitivity and liver function improvement. This radar plot is a comparative snapshot of molecular mechanism coverage addressed by pioglitazone derivatives. Inflammatory mechanisms and mitochondrial mechanisms were emphasized in liver-targeting research (blue) and were addressed more comprehensively in pancreatic research (red) with PPARγ activation and epigenetic regulation. This bar chart compares relative statistical strength of evidence in pioglitazone action in inflammatory and functional pathways. Liver-targeted studies (blue) were more significant in TNF-α, IL-6, IL-1β, and ER stress reduction, while pancreas-targeted studies (red) were more significant in insulin sensitivity improvement and liver function. Larger –log(p-value) is larger statistical significance.

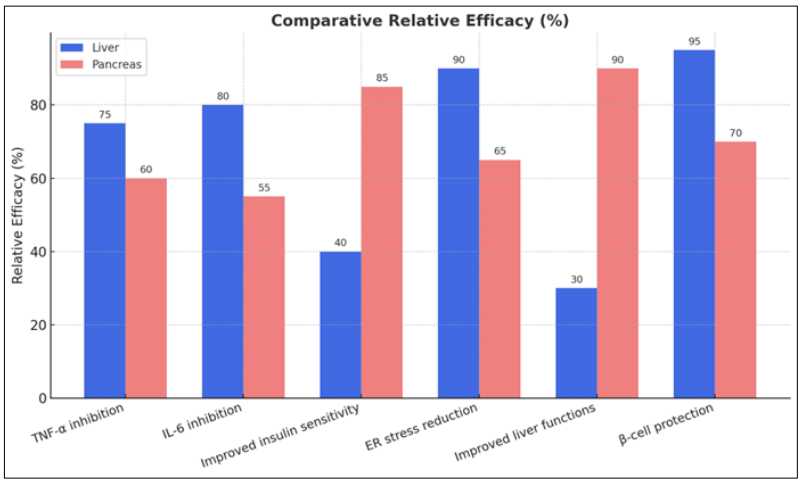

Fig. 5. Comparative relative efficacy (%) of pioglitazone: liver vs. pancreas

Two recent experimental studies, were selected to make the most mechanistically informative and experimentally balanced comparison between pancreatic and hepatic thiazole derivatives. The first study examined the thiazol-sulfonyl analogue (KM9) in zebrafish liver models, presenting comprehensive molecular evidence of hepatic insulin pathway regeneration, inhibition of inflammation, and antioxidant activation. By contrast, second study tested rhodanine–thiazole hybrids against pancreatic enzymatic and receptor-level mechanisms, such as Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) activation and inhibition of α-amylase/α-glucosidase. Cumulatively, the studies support a robust and complementary concept of the dual-organ action of thiazole derivatives-the hepatic modulation of metabolism and pancreatic regulation of insulin dynamics-worthy of the inclusion of the derivatives in this comparative review. The KM9 thiazol-sulfonyl analogue restored insulin cascades in zebrafish liver models through the regulation of insulin receptor gene expression and lipogenesis inhibition through SREBP1 and FASN downregulation. It also lowered lipid deposition to a great extent and inhibited NF-κB–induced inflammatory cascades, reducing TNF-α and IL-6 levels and inhibiting macrophage migration. Furthermore, KM9 increased antioxidant defense by raising SOD, CAT, GST, and GPx activity to a very significant extent with strong multi-level hepatoprotective mechanisms. Rhodanine–thiazole hybrids PPAR-γ was activated dose-dependently to increase insulin sensitivity and associated signaling. They also inhibited α-amylase and α-glucosidase by mixed-type inhibition. Results were, however, qualitatively predominant with little fold-change data and poor statistical testing, reducing their mechanistic detail Fig. 6 [24, 25].

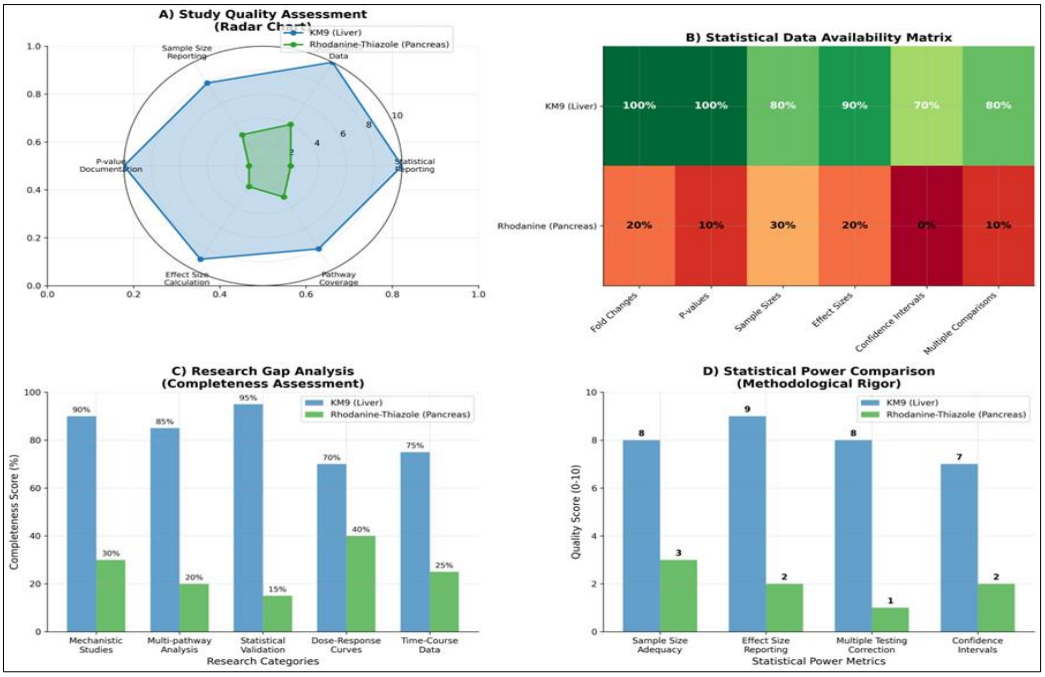

Fig. 6. Comparative quality, research gaps, and statistical power assessment of hepatic (KM9) vs. pancreatic

The results in this Fig. 6. shown comparison of thiazole derivative studies' methodological quality and statistical power. Panel A: Radar chart summarizing study quality across the board, where KM9 (liver) provided better coverage across all parameters compared to rhodanine–thiazole (pancreas). Panel B: Availability matrix of statistical information indicating that KM9 provided fold-changes, p-values, sample sizes, effect sizes, and confidence intervals in both instances, but the pancreatic study was poorly documented. Panel C: Comparison of studies by gap analysis, where KM9 well-rated on completeness of mechanism studies, multi-pathway analysis, validation statistics, dose-response plots, and time-course data, but the pancreatic study still limited. Panel D: Comparison of statistical power, where KM9 more sound methodologically with improved scores on sample size sufficiency, reporting effect sizes, multiple testing adjustment, and confidence intervals.

4. Conclusion

Thiazole/thiazolidinedione derivatives display complementary organ-differentiated effects in mechanistic, clinical, and molecular contexts. Pancreatic-directed molecules produce faster and more potent glycemic responses (↑ insulin secretion by 4-fold, ↓ glucose and HOMA-IR) and direct β-cell preservation, whereas hepatic-directed molecules produce more sustained effects (less fluctuation), more selective anti-inflammatory/anti-oxidative signaling, and long-term metabolic robustness (↑ C-peptide, ↓ ALT/AST, improved insulin sensitivity). Clinical evidence is more advanced along the hepatic axis (larger cohorts and longer follow-up), with pancreatitis trials providing cleaner mechanistic data but weaker cohorts and worse statistics. In all, the optimal approach is a two-pathway approach—add hepatic protection with pancreatic stimulation—delivered by standardized biomarker panels, better statistics (effect sizes, CIs, multiplicity control), and integrated liver–pancreas designs. Future work should expand PI3K/Akt, MAPK, and AMPK coverage, include epigenetic profiling, extend follow-up, and prioritize unified trials to maximize translational impact in diabetes care.

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Nomenclature & Symbols

TZD(s)	Thiazolidinedione(s)	TNF-α	Tumor Necrosis Factor-alpha
C-peptide	Connecting Peptide	IL-1β	Interleukin-1 beta
FPG	Fasting Plasma Glucose	NF-κB	Nuclear Factor kappa-B
β-cell	Beta cell	HbA1c	Hemoglobin A1c

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