ABHINAV MISHRA - M.SC. BIOINFORMATICS - MATRICULATION: 5491552

A Physiologically-Based Pharmacokinetic Model of Tirzepatide

Abstract

Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, represents a novel approach for treating type 2 diabetes mellitus (T2DM) and obesity. By combining the actions of both incretins, it enhances insulin secretion, suppresses glucagon, and reduces appetite, leading to superior glycemic control and weight loss compared to traditional GLP-1 receptor agonists. Despite its efficacy, inter-individual variability in pharmacokinetics necessitates a mechanistic understanding for optimized therapeutic application. This study employs physiologically-based pharmacokinetic (PBPK) modeling to characterize tirzepatide's absorption, distribution, metabolism, and excretion (ADME). The model integrates physiological parameters to assess dose proportionality, hepatic and renal impairment effects, and body weight dependency. By improving drug exposure predictions, this approach aids personalized treatment strategies and enhances clinical decision-making across diverse patient populations.

Keywords: GLP-1; Tirzepatide; Diabetes; Pharmacokinetics; PBPK; GIP; DPP-4; Metabolism; Renal; Hepatic

1 Introduction

1.1 GLP-1 Agonists and Tirzepatide

GLP-1 receptor agonists (GLP-1 RAs) are key in treating type 2 diabetes and obesity, improving glycemic control, weight management, and cardiovascular health [1]. However, native GLP-1 degrades rapidly due to dipeptidyl peptidase-4 (DPP-4), limiting its therapeutic potential. To counter this, GLP-1 RAs like exenatide and semaglutide were developed for prolonged action, though they have side effects and variable efficacy [2, 3].

Tirzepatide, a dual GIP and GLP-1 receptor agonist, enhances insulin secretion, suppresses glucagon, and improves insulin sensitivity [4]. Clinical trials show it outperforms GLP-1 RAs in HbA1c and weight reduction [5, 1]. Its once-weekly dosing improves adherence, but responses vary due to metabolic differences [6].

Given tirzepatide's complex pharmacokinetics (PK) and growing clinical applications, a physiologically-based pharmacokinetic (PBPK) model offers a mechanistic framework to assess its absorption, distribution, metabolism, and excretion (ADME) [6, 7]. This approach helps optimize dosing, particularly for patients with impaired organ function, and supports personalized treatment strategies. As tirzepatide's clinical applications expand, PBPK modeling will be vital in refining its therapeutic use.

1.2 Tirzepatide Pharmacokinetics

Tirzepatide, a dual GIP and GLP-1 receptor agonist for T2DM and obesity, has a long half-life enabling once-weekly dosing. Administered subcutaneously in the abdomen, thigh, or upper arm, it is slowly absorbed, reaching peak plasma levels (T_{max}) in 24–72 hours. With high plasma protein binding (∼99%) and a large volume of distribution, it remains in circulation for an extended period. It undergoes proteolytic degradation by DPP-4 and NEP rather than CYP enzymes, minimizing drug interactions. Its elimination half-life ($T_{1/2}$) is 5 days (120 hours), with clearance primarily via proteolysis and minimal excretion of the intact molecule.

1.2.1 Dose Proportionality

Tirzepatide displays dose-proportional pharmacokinetics across the therapeutic dose range of 2.5 mg to 15 mg, with linear increases in systemic exposure (C_{max} and AUC) as the dose increases (Fig. 6).

1.2.2 Impact of Hepatic and Renal Impairment

Tirzepatide's pharmacokinetics are minimally affected by hepatic and renal impairment. Since it is not metabolized through the CYP system, mild to moderate hepatic impairment has little impact on its pharmacokinetics, though data on severe hepatic impairment remain limited. Similarly, studies indicate that mild to severe renal impairment does not significantly alter tirzepatide exposure, as its elimination primarily occurs through peptide metabolism rather than direct renal excretion (Fig. 7, 8).

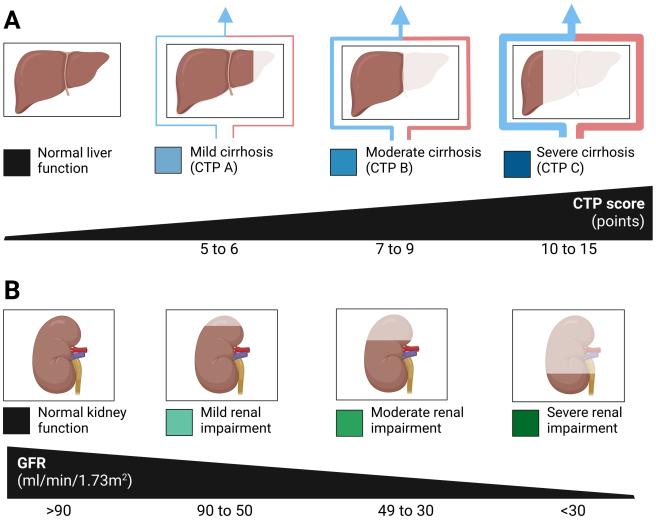


Figure 1: Cirrhosis and renal impairments in relation to tirzepatide metabolism. The Child-Turcotte-Pugh (CTP) score assesses hepatic function in cirrhosis, while the glomerular filtration rate (GFR) measures renal impairment. Both factors influence tirzepatide metabolism and excretion.

1.2.3 Special Populations

Tirzepatide pharmacokinetics remain consistent across age and gender, with no clinically significant differences between younger and older adults or between males and females.

2 Scientific Questions

This project aims to comprehensively study tirzepatide's pharmacokinetic and pharmacodynamic profiles. Using computational modeling, pharmacokinetic data analysis, and patient-specific parameters, we will address critical factors driving inter-individual variability in response to these therapies. A particular focus will be placed on patients with hepatic and renal impairments, given their altered metabolism and excretion pathways. The outcomes of this research will contribute to the development of predictive models and support precision medicine approaches, optimizing the clinical use of tirzepatide for diverse patient populations.

1 Establish pharmacokinetics database of tirzepatide for model building and validation

2 Develop a computational model of tirzepatide (physiological based whole-body model)

3 Study the effect of renal and hepatic impairment on tirzapetide pharmacokinetics

3 Methods

This study employed a structured methodological approach, consisting of a systematic review of the literature to compile pharmacokinetic data for tirzepatide (Sec. 3.1); curation of clinical data to ensure accuracy and relevance for

analysis (Sec. 3.2); construction and implementation of a physiologically based pharmacokinetic (PBPK) model to characterize the drug's pharmacokinetic behavior (Sec. 3.3); optimization of model parameters using clinical datasets (Sec. 3.4); and calculation of pharmacokinetic parameters to validate the model and support its interpretation (Sec. 3.5).

3.1 Systematic literature research

A systematic literature search was conducted to identify studies reporting pharmacokinetic data for tirzepatide. Searches were performed on PubMed using the keywords `tirzepatide AND pharmacokinetics` and the PKPDAI database [8], accessed on 2024-12-17. The search initially identified several studies related to tirzepatide's pharmacokinetics. Articles were screened based on predefined inclusion and exclusion criteria (Fig. 2):

- **Inclusion criteria:** Clinical trials involving healthy volunteers or patients with T2DM, as well as studies investigating the effects of renal and hepatic impairments on tirzepatide pharmacokinetics.
- **Exclusion criteria:** Studies involving pediatric populations, non-human subjects, or insufficiently reported pharmacokinetic parameters.

3.2 Data curation

Selected literature data were curated and stored in the open pharmacokinetics database PK-DB [9], following established protocols [9]. Relevant patient-specific details, including age, sex, comorbidities, medications, dosing regimens, and pharmacokinetic profiles, were extracted. Pharmacokinetic figures were digitized using WebPlotDigitizer [10], and tabular/textual data were standardized for consistency [9].

Patient data were categorized by demographics and clinical factors, ensuring uniformity. Key pharmacokinetic parameters (C_{max}, T_{max}, $T_{1/2}$) and pharmacodynamic markers (glucose, insulin) were included for PBPK modeling. The curated dataset formed the basis for model construction, calibration, and validation, with all data accessible via PK-DB [9]. An overview of included studies is shown in Tab. 1.

3.3 Model

The PBPK model and tissue-specific submodels were developed using the Systems Biology Markup Language (SBML) [11, 12]. Programmatic manipulation and visualization of the models were performed using the `sbmlutils` [13] and `cy3sbml` [14] libraries. Numerical solutions for the ordinary differential equations (ODEs) underlying the model were computed using `sbmlsim` [15], powered by the high-performance SBML simulation engine `libRoadRunner` [16, 17]. The model is publicly available in SBML format under a CC-BY 4.0 license, with all associated equations accessible at `https://github.com/matthiaskoenig/tirzepatide-model`. The specific version used in this project is 0.9.3 [18] (Fig. 3).

Hepatic Impairment Hepatic function was modeled using the scaling parameter `LI__f_hepatic_function`, where 1.0 represents normal function and lower values indicate impairment. Severity was classified using the Child-Pugh system, with scaling factors for mild (0.399), moderate (0.698), and severe cirrhosis (0.813). These were applied to hepatic metabolism to simulate reduced drug clearance [19, 20].

Renal Impairment Renal function was modeled via `KI__f_renal_function`, with 1.0 as normal and lower values reflecting impairment. Following KDIGO guidelines, scaling factors were set for mild (0.5), moderate (0.35), severe (0.20), and end-stage (0.1) impairment [21]. These adjustments accounted for reduced glomerular filtration, tubular secretion, and reabsorption of tirzepatide and its metabolites (Fig. 1).

3.4 Parameter optimization

Parameter fitting was conducted to minimize the discrepancy between experimental data and model predictions by optimizing ten key parameters related to application, proteolytic cleavage, and excretion processes. The optimized parameters are detailed in Tab. 2.

The optimization process utilized a combined dataset encompassing single and multiple dose studies, and multiple runs ($n = 100$) were performed using a local optimizer with different initial parameter conditions to ensure convergence. The best-fit parameters were selected for the final model, and are shown in Tab. 2.

3.5 Pharmacokinetic parameters

Pharmacokinetic parameters for tirzepatide were derived from plasma concentration-time profiles and urinary excretion data using standard non-compartmental analysis methods [22].

4 Results

4.1 Tirzepatide data

The initial step in developing the PBPK model involved the curation of data from clinical studies. Articles were selected based on a systematic literature search, focusing on publications that included time-course data and pharmacokinetic parameters for tirzepatide. This search identified 4 studies from PKPDAI and 20 studies from PubMed. An additional 23 studies were manually added. The workflow for this curation process is illustrated in Fig. 2.

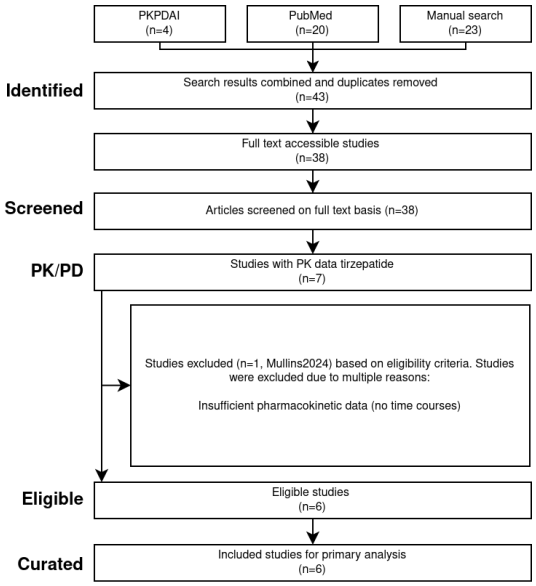


Figure 2: PRISMA flow diagram. Overview of data selection for the pharmacokinetics dataset of tirzepatide established. PubMed, PKPDAI, and manual searches were used for the literature search. Application of the eligibility criteria resulted in 6 studies, which were curated for this work (see Tab. 1).

Table 1: Overview of tirzepatide studies. This table includes key identifiers (*Study*, *PMID*, *PK-DB ID*), administration route (*Route*), dosing regimen (*Dosing*) and dose (*Dose*), and participant characteristics (*H* for healthy, *RI* for renal impairment, *HI* for hepatic impairment, *T2* for diabetes mellitus type 2).

Study	PMID	PK-DB ID	Route	Dosing	Dose [mg]	H	RI	HI	T2
Coskun2018	30473097	PKDB00967	SC	single, multiple	0.25 - 15	✓	-	-	✓
Feng2023	37285081	PKDB00962	SC	multiple	2.5 - 15	-	-	-	✓
Furihata2022	34647404	PKDB00964	SC	multiple	2.5 - 15	-	-	-	✓
Martin2024	39243911	PKDB00968	SC	single	4.1	✓	-	-	-
Urva2021	33778934	PKDB00963	SC	single	5	-	✓	-	✓
Urva2022	35674880	PKDB00969	SC	single	5	-	-	✓	✓

In total, 6 clinical studies met the criteria and were selected for the development and evaluation of the PBPK model. These studies provided comprehensive pharmacokinetic data under various conditions, including detailed information on dosing protocols, administration routes, participant health status, co-administered drugs, and study design. Each study was assigned a unique identifier in the PK-DB database (PK-DB ID) and linked to its corresponding PubMed ID (PMID), ensuring easy traceability.

The curated dataset was made publicly available as open data to promote transparency and reproducibility. A summary of the selected studies, including key details such as participant characteristics and drug administration protocols, is shown in Tab. 1.

4.2 Computational model

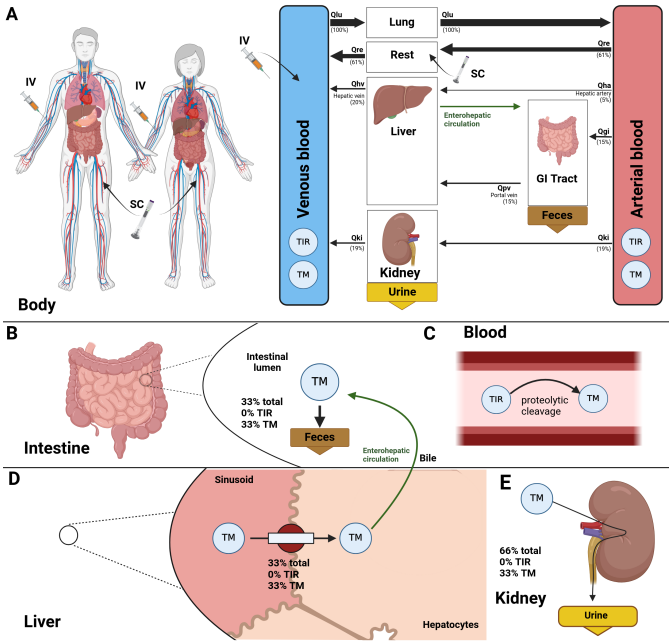


Figure 3: Physiologically based pharmacokinetic (PBPK) model of tirzepatide. A) Whole-body model illustrating systemic circulation via venous and arterial blood, with key organs (liver, kidney, GI tract) involved in tirzepatide's (TIR) metabolism, distribution, and excretion. **B)** Intestinal model showing the excretion via feces after enterohepatic circulation. Approximately 33% of the dose is excreted via feces. **C)** Proteolytic cleavage of TIR in the blood, resulting in the formation of tirzepatide metabolites (TM). **D)** Uptake and enterohepatic circulation of tirzepatide metabolites (TM) in the liver. TM is excreted via the bile. **E)** Renal model highlighting the elimination of metabolites, approximately 66% of the dose, via urine, with no unchanged TIR detected in urine.

Using the curated dataset of pharmacokinetic studies for tirzepatide, a PBPK model was developed to simulate the pharmacokinetics of the drug. This model was designed to provide detailed insight into absorption, distribution, metabolism and excretion under various physiological and pathological conditions.

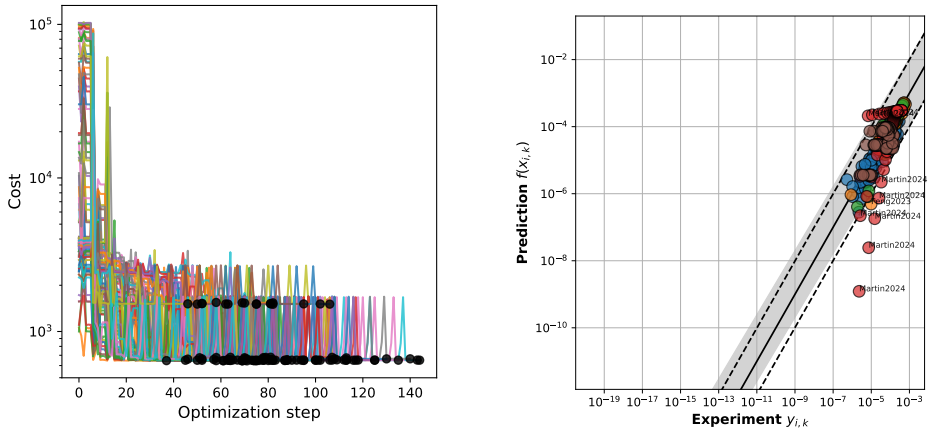
The model integrates the systemic circulation with detailed representations of key tissues involved in the pharmacokinetics of tirzepatide. These include the gastrointestinal tract, liver and kidneys, as shown in Fig. 3. Tissue-specific models were combined into a whole-body framework, allowing simulations to consider both localized processes and how they interact within the systemic circulation.

4.3 Parameter optimization

Table 2: Optimized parameters for the tirzepatide PBPK model.

Parameter name	Description	Value	Unit
Ksc_tir	Subcutaneous absorption rate of tirzepatide	0.3284E-3	1/min
TIR2TM_k	Rate for tirzepatide cleavage in plasma	0.6782E-3	l/min
KI__TMEX_k	Rate for TM renal excretion	19.19E-3	l/min
LI__TMEX_k'	Rate for TM liver excretion	3.949E-3	l/min
GU__TMEXC_k	Rate for TM fecal excretion	0.3920E-3	l/min

Parameter optimization enhanced the model's agreement with the data. Figure 4 shows the convergence of the optimization algorithm, demonstrating its effectiveness in minimizing the error, and a scatter plot comparing the



Error convergence Goodness-of-fit

Figure 4: Optimization Performance.

model's predictions to the actual data points, visually confirming the improved goodness-of-fit achieved through parameter optimization.

4.4 Prediction of Clinical Studies

The PBPK model, calibrated using the optimized parameters in Tab. 2, was employed to simulate clinical study outcomes, as depicted in Fig. 5. The model effectively replicates plasma concentration-time profiles observed across multiple independent studies, capturing key pharmacokinetic properties of tirzepatide, including its prolonged half-life and dose-proportional absorption kinetics.

Simulation results closely align with experimental data, demonstrating the model's ability to predict drug exposure under different physiological conditions, including renal and hepatic impairment.

4.5 Dose dependency

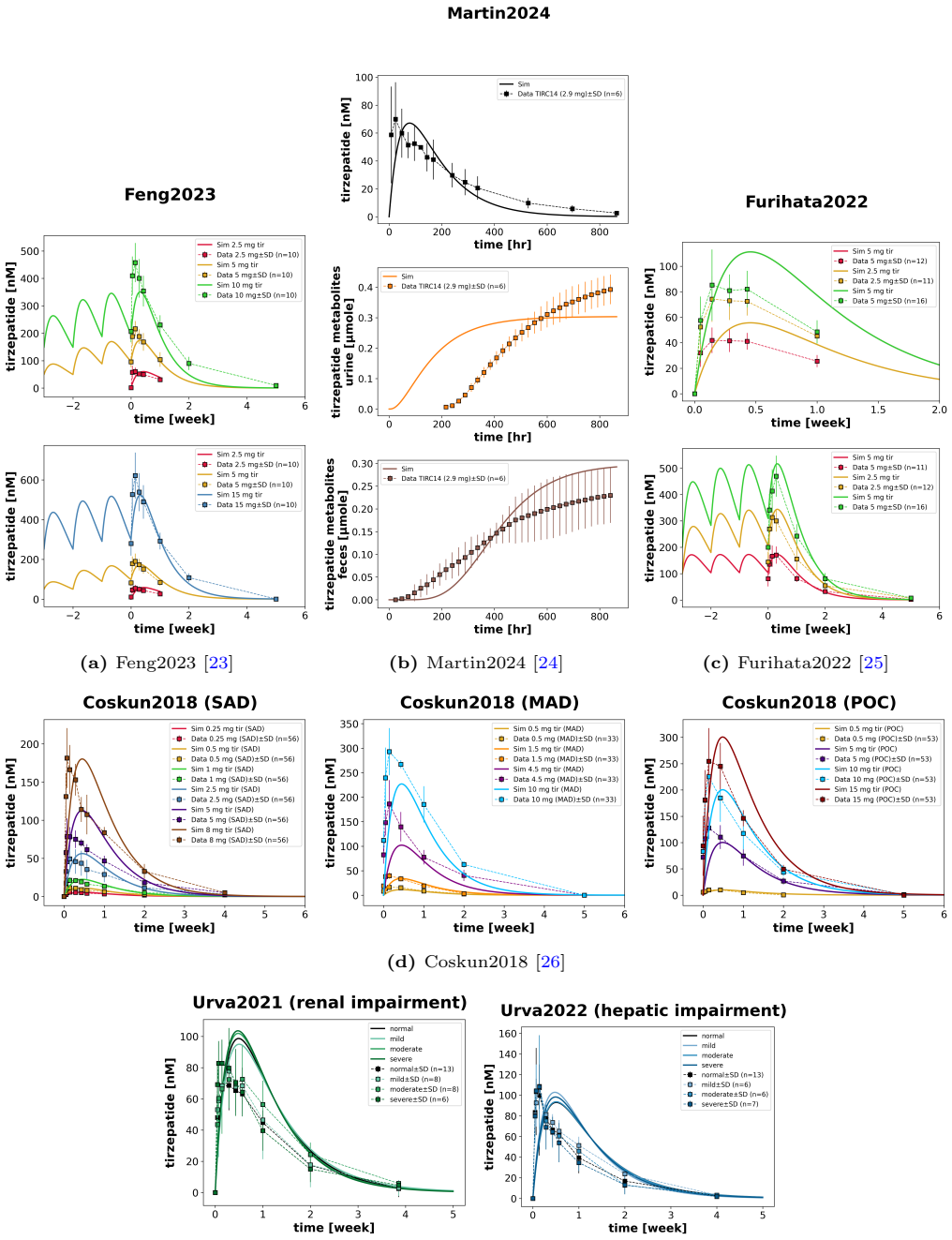
Following parameter optimization, the model was used to explore the dose-dependent pharmacokinetics of tirzepatide. The simulations demonstrated a proportional increase in systemic exposure with escalating doses, confirming dose linearity across the therapeutic range. Steady-state concentrations were reached after approximately three weeks of continuous administration. The excretion profile showed a elimination of metabolites via the renal route and fecal route (Fig. 6).

4.6 Hepatic impairment

To assess the impact of hepatic dysfunction on tirzepatide metabolism, simulations were conducted using hepatic impairment scaling factors based on Child-Turcotte-Pugh (CTP) classification. The results indicated a moderate increase in systemic exposure in patients with severe cirrhosis, though the overall elimination profile remained consistent with healthy individuals. These findings align with clinical observations suggesting that hepatic impairment has a limited effect on tirzepatide clearance (Fig. 7).

4.7 Renal impairment

Renal elimination is a major pathway for tirzepatide metabolites. Simulations incorporating various degrees of renal impairment, classified by estimated glomerular filtration rate (GFR), revealed a progressive increase in drug exposure with worsening renal function. However, since tirzepatide itself is not excreted unchanged in urine, only its metabolites exhibited significant accumulation in individuals with severe renal dysfunction (Fig. 8).



(a) Feng2023 [23] **(b)** Martin2024 [24] **(c)** Furihata2022 [25]

(d) Coskun2018 [26]

(e) Urva2021 [27] **(f)** Urva2022 [28]

Figure 5: Comparison of model simulations with observed data from studies. Data from [23, 25, 26, 24, 27, 28]. **MAD**: Multiple-ascending dose, **SAD**: Single-ascending dose, and **POC**: Proof-of-concept

4.8 Bodyweight dependency

Given the role of body weight in drug distribution and clearance, simulations were performed across a range of body mass indices (BMIs). The results suggested that higher body weight slightly reduces tirzepatide plasma concentrations due to increased distribution volume. The influence of body weight on renal and hepatic metabolism was also investigated, confirming that adjustments in dosing are unlikely to be required based solely on patient weight (Fig. 9a, 9b).

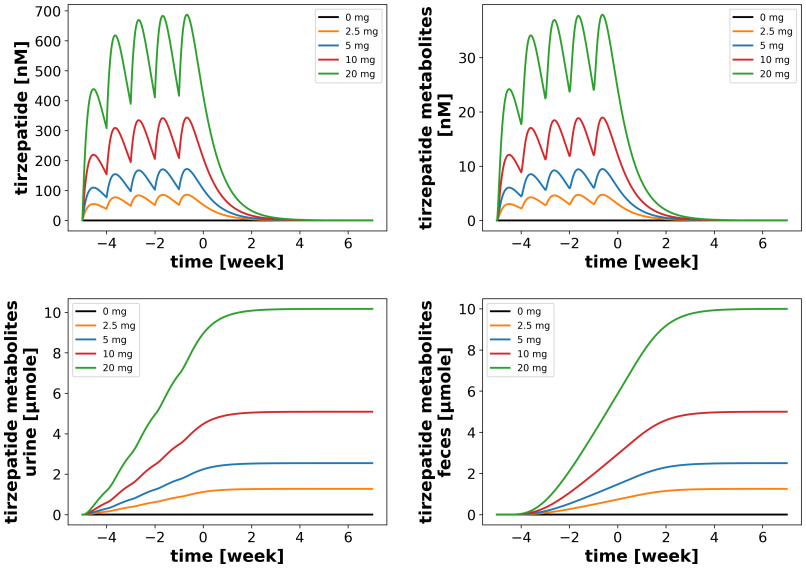


Figure 6: Dose-dependent effects of tirzepatide administered subcutaneously. The top row shows that both tirzepatide (left) and its metabolites (right) reach steady-state concentrations after 3 weeks. The bottom row illustrates metabolite elimination, with excretion via urine (left) and via feces (right).

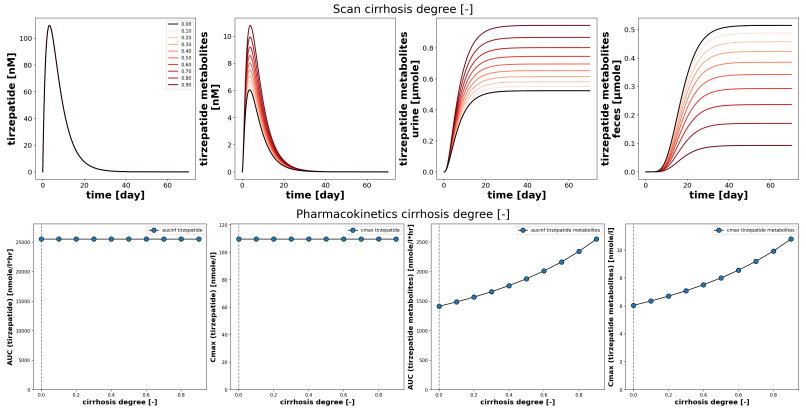


Figure 7: Impact of hepatic impairment on tirzepatide pharmacokinetics. Scan of tirzepatide plasma concentration-time profiles and pharmacokinetic parameters show no significant differences across varying degrees of hepatic impairment classified by CTP scores, suggesting that hepatic dysfunction does not alter tirzepatide metabolism or clearance, indicating no need for dose adjustments in cirrhotic patients (Fig. 1)

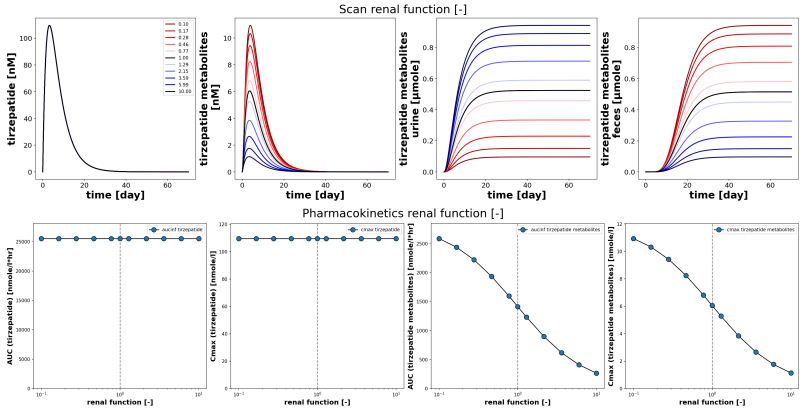
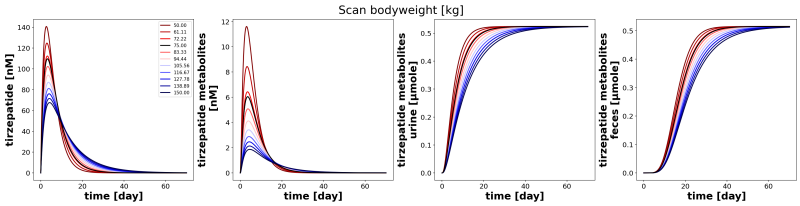


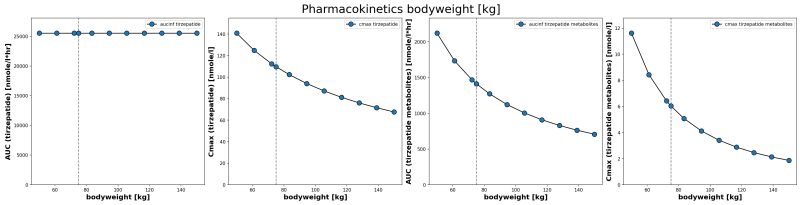
Figure 8: Impact of renal impairment on tirzepatide pharmacokinetics. A progressive increase in tirzepatide metabolite concentrations with declining renal function, while the parent drug remains largely unaffected. (C_{max} and AUC) exhibit an asymptotic relationship with renal function, suggesting that severe impairment leads to saturation-like effects on systemic exposure (Fig. 1).

5 Discussion

This study presents a mechanistic framework for understanding tirzepatide's pharmacokinetics under various conditions. The model accurately captured key ADME processes, reflecting its dose-proportional kinetics and extended half-life (Fig. 3, 5). Hepatic dysfunction did not alter tirzepatide metabolism or clearance, indicating no need for



(a) Bodyweight dependency.



(b) Parameter dependency for pharmacokinetic parameters.

Figure 9: Body weight influence on tirzepatide pharmacokinetics.

dose adjustments in cirrhotic patients (Fig. 7). In contrast, severe renal impairment led to saturation-like effects on systemic exposure, with progressive accumulation of tirzepatide metabolites, highlighting the need for careful monitoring in patients with advanced renal dysfunction (Fig. 8). While higher body weight slightly reduced C_{max} for tirzepatide and its metabolites, it had a more pronounced effect on AUC for tirzepatide metabolites (Fig. 9). The model's strong agreement with clinical data supports its utility in optimizing dosing strategies (Fig. 4).

6 Abbreviations

ODE: Ordinary differential equations, **SBML**: Systems biology markup language, **ADME**: Absorption, Distribution, Metabolism, and Excretion, **AUC**: Area Under the Curve, **CC-BY**: Creative Commons Attribution, **CL/F**: Apparent Clearance, **CPT**: Child-Pugh Classification, **CV**: Coefficient of Variation, **CYP**: Cytochrome P450, **DPP-4**: Dipeptidyl Peptidase-4, **GIP**: Glucose-Dependent Insulinotropic Polypeptide, **GLP**: Glucagon-Like Peptide, **GLP-1**: Glucagon-Like Peptide-1, **GLP-1 RA**: Glucagon-Like Peptide-1 Receptor Agonist, **HbA1c**: Hemoglobin A1c, **KDIGO**: Kidney Disease: Improving Global Outcomes, **LI**: Liver Impairment (as a parameter in PBPK model), **NEP**: Neutral Endopeptidase, **ODE**: Ordinary Differential Equation, **PBPK**: Physiologically-Based Pharmacokinetic, **PD**: Pharmacodynamics, **PK**: Pharmacokinetics, **PK-DB**: Pharmacokinetics Database, **PKPDAI**: Pharmacokinetics and Pharmacodynamics Artificial Intelligence Database, **PMID**: PubMed Identifier, **PRISMA**: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, **SBML**: Systems Biology Markup Language, **T2DM**: Type 2 Diabetes Mellitus, **TIR**: Tirzepatide (used as a shorthand in the model), V_d: Volume of Distribution, $t_{1/2}$: Elimination Half-Life, T_{max}: Time to Maximum Plasma Concentration, C_{max}: Maximum Plasma Concentration, **F**: Bioavailability (as used in pharmacokinetics equations).

7 Contributions

Abhinav Mishra (AM) conducted the research internship, contributing significantly to the development and refinement of the physiologically-based pharmacokinetic (PBPK) model for tirzepatide. AM was responsible for conducting a systematic literature review to identify and curate pharmacokinetic data from clinical studies, ensuring a comprehensive dataset for model development. Additionally, AM developed and implemented parameter optimization strategies for curated studies to enhance the predictive accuracy of the PBPK model. Numerical simulations were performed to evaluate tirzepatide's pharmacokinetics across different patient populations, with a particular focus on renal and hepatic impairment. Furthermore, AM investigated dose dependency, body weight effects, and physiological variability to support personalized treatment strategies. To ensure clarity and scientific rigor, AM also wrote and structured the research report, detailing the methodology, model validation, and key findings. Matthias König (MK) supervised the project, providing guidance on model development, optimization strategies, and pharmacokinetic analysis. MK also contributed to the conceptualization of the study, the interpretation of simulation results, and proofreading the report.

8 Acknowledgments

This work was supervised by Matthias König (MK) https://livermetabolism.com. MK was supported by the BMBF within ATLAS by grant number 031L0304B and the German Research Foundation (DFG) within the Research Unit Program FOR 5151 QuaLiPerF by grant number 436883643 and by grant number 465194077 (Priority Programme SPP 2311, Subproject SimLivA). This work was supported by the BMBF-funded de.NBI Cloud within the German Network for Bioinformatics Infrastructure (de.NBI) (031A537B, 031A533A, 031A538A, 031A533B, 031A535A, 031A537C, 031A534A, 031A532B).

References

1. Drucker, D.J.: Efficacy and Safety of GLP-1 Medicines for Type 2 Diabetes and Obesity. **47**(11), 1873–1888. doi:10.2337/dci24-0003. 38843460

2. Bays, H.E., Fitch, A., Christensen, S., Burridge, K., Tondt, J.: Anti-Obesity Medications and Investigational Agents: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022. **2**, 100018. doi:10.1016/j.obpill.2022.100018. 37990711

3. Chavda, V.P., Ajabiya, J., Teli, D., Bojarska, J., Apostolopoulos, V.: Tirzepatide, a New Era of Dual-Targeted Treatment for Diabetes and Obesity: A Mini-Review **27**(13), 4315. doi:10.3390/molecules27134315. 35807558

4. Mariam, Z., Niazi, S.K.: Glucagon-like peptide agonists: A prospective review. **7**(1), 462. doi:10.1002/edm2.462. 38093651

5. Tang, Y., Zhang, L., Zeng, Y., Wang, X., Zhang, M.: Efficacy and safety of tirzepatide in patients with type 2 diabetes: A systematic review and meta-analysis **13**, 1016639. doi:10.3389/fphar.2022.1016639. 36569320

6. Dubbelboer, I.R., Sjögren, E.: Physiological based pharmacokinetic and biopharmaceutics modelling of subcutaneously administered compounds – An overview of in silico models **621**, 121808. doi:10.1016/j.ijpharm.2022.121808. Accessed 2025-01-09

7. Skelley, J.W., Swearengin, K., York, A.L., Glover, L.H.: The impact of tirzepatide and glucagon-like peptide 1 receptor agonists on oral hormonal contraception **64**(1), 204–2114. doi:10.1016/j.japh.2023.10.037. 37940101

8. Gonzalez Hernandez, F., Carter, S.J., Iso-Sipilä, J., Goldsmith, P., Almousa, A.A., Gastine, S., Lilaonitkul, W., Kloprogge, F., Standing, J.F.: An automated approach to identify scientific publications reporting pharmacokinetic parameters **6**, 88. doi:10.12688/wellcomeopenres.16718.1. Accessed 2024-04-24

9. Grzegorzewski, J., Brandhorst, J., Green, K., Eleftheriadou, D., Duport, Y., Barthorscht, F., Köller, A., Ke, D.Y.J., De Angelis, S., König, M.: PK-DB: Pharmacokinetics database for individualized and stratified computational modeling **49**(D1), 1358–1364. doi:10.1093/nar/gkaa990. 33151297

10. Rohatgi, A.: WebPlotDigitizer. https://automeris.io

11. Hucka, M., Bergmann, F.T., Chaouiya, C., Dräger, A., Hoops, S., Keating, S.M., König, M., Novère, N.L., Myers, C.J., Olivier, B.G., Sahle, S., Schaff, J.C., Sheriff, R., Smith, L.P., Waltemath, D., Wilkinson, D.J., Zhang, F.: The Systems Biology Markup Language (SBML): Language Specification for Level 3 Version 2 Core Release 2 **16**(2). doi:10.1515/jib-2019-0021. Accessed 2024-04-19

12. Keating, S.M., Waltemath, D., König, M., Zhang, F., Dräger, A., Chaouiya, C., Bergmann, F.T., Finney, A., Gillespie, C.S., Helikar, T., Hoops, S., Malik-Sheriff, R.S., Moodie, S.L., Moraru, I.I., Myers, C.J., Naldi, A., Olivier, B.G., Sahle, S., Schaff, J.C., Smith, L.P., Swat, M.J., Thieffry, D., Watanabe, L., Wilkinson, D.J., Blinov, M.L., Begley, K., Faeder, J.R., Gómez, H.F., Hamm, T.M., Inagaki, Y., Liebermeister, W., Lister, A.L., Lucio, D., Mjolsness, E., Proctor, C.J., Raman, K., Rodriguez, N., Shaffer, C.A., Shapiro, B.E., Stelling, J., Swainston, N., Tanimura, N., Wagner, J., Meier-Schellersheim, M., Sauro, H.M., Palsson, B., Bolouri, H., Kitano, H., Funahashi, A., Hermjakob, H., Doyle, J.C., Hucka, M., SBML Level 3 Community members: SBML Level 3: An extensible format for the exchange and reuse of biological models **16**(8), 9110. doi:10.15252/msb.20199110. 32845085

13. König, M.: Sbmlutils: Python Utilities For SBML. doi:10.5281/ZENODO.13325770. Zenodo. https://zenodo.org/doi/10.5281/zenodo.13325770 Accessed 2024-09-13

14. König, M., Dräger, A., Holzhütter, H.-G.: CySBML: A Cytoscape plugin for SBML **28**(18), 2402–2403. doi:10.1093/bioinformatics/bts432. Accessed 2024-04-19

15. König, M.: Sbmlsim: SBML Simulation Made Easy. doi:10.5281/ZENODO.5531088. [object Object]. https://zenodo.org/record/5531088 Accessed 2024-04-19

16. Welsh, C., Xu, J., Smith, L., König, M., Choi, K., Sauro, H.M.: libRoadRunner 2.0: A high performance SBML simulation and analysis library **39**(1), 770. doi:10.1093/bioinformatics/btac770. Accessed 2024-04-19

17. Somogyi, E.T., Bouteiller, J.-M., Glazier, J.A., König, M., Medley, J.K., Swat, M.H., Sauro, H.M.: libRoadRunner: A high performance SBML simulation and analysis library **31**(20), 3315–3321. doi:10.1093/bioinformatics/btv363. Accessed 2024-04-19

18. Mishra, A., König, M.: Physiologically Based Pharmacokinetic (PBPK) Model of Tirzepatide. Zenodo. https://doi.org/10.5281/zenodo.14984688

19. Child, C.G., Turcotte, J.G.: Surgery and portal hypertension **1**, 1–85. 4950264

20. Infante-Rivard, C., Esnaola, S., Villeneuve, J.-P.: Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics **7**(4), 660–664. doi:10.1002/hep.1840070408. Accessed 2025-01-13

21. Stevens, P.E., Ahmed, S.B., Carrero, J.J., Foster, B., Francis, A., Hall, R.K., Herrington, W.G., Hill, G., Inker, L.A., Kazancıoğlu, R., Lamb, E., Lin, P., Madero, M., McIntyre, N., Morrow, K., Roberts, G., Sabanayagam, D., Schaeffner, E., Shlipak, M., Shroff, R., Tangri, N., Thanachayanont, T., Ulasi, I., Wong, G., Yang, C.-W., Zhang, L., Levin, A.: KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease **105**(4), 117–314. doi:10.1016/j.kint.2023.10.018. Accessed 2024-04-22

22. Köller, A., Grzegorzewski, J., Tautenhahn, H.-M., König, M.: Prediction of Survival After Partial Hepatectomy Using a Physiologically Based Pharmacokinetic Model of Indocyanine Green Liver Function Tests **12**, 730418. doi:10.3389/fphys.2021.730418. Accessed 2024-04-22

23. Feng, P., Sheng, X., Ji, Y., Urva, S., Wang, F., Miller, S., Qian, C., An, Z., Cui, Y.: A Phase 1 Multiple Dose Study of Tirzepatide in Chinese Patients with Type 2 Diabetes. **40**(8), 3434–3445. doi:10.1007/s12325-023-02536-8. 37285081

24. Martin, J.A., Czeskis, B., Urva, S., Cassidy, K.C.: Absorption, distribution, metabolism, and excretion of tirzepatide in humans, rats, and monkeys. **202**, 106895. doi:10.1016/j.ejps.2024.106895. 39243911

25. Furihata, K., Mimura, H., Urva, S., Oura, T., Ohwaki, K., Imaoka, T.: A phase 1 multiple-ascending dose study of tirzepatide in Japanese participants with type 2 diabetes. **24**(2), 239–246. doi:10.1111/dom.14572. 34647404

26. Coskun, T., Sloop, K.W., Loghin, C., Alsina-Fernandez, J., Urva, S., Bokvist, K.B., Cui, X., Briere, D.A., Cabrera, O., Roell, W.C., Kuchibhotla, U., Moyers, J.S., Benson, C.T., Gimeno, R.E., D'Alessio, D.A., Haupt, A.: LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept **18**, 3–14. doi:10.1016/j.molmet.2018.09.009. 30473097

27. Urva, S., Quinlan, T., Landry, J., Martin, J., Loghin, C.: Effects of Renal Impairment on the Pharmacokinetics of the Dual GIP and GLP-1 Receptor Agonist Tirzepatide. **60**(8), 1049–1059. doi:10.1007/s40262-021-01012-2. 33778934

28. Urva, S., Quinlan, T., Landry, J., Ma, X., Martin, J.A., Benson, C.T.: Effects of Hepatic Impairment on the Pharmacokinetics of the Dual GIP and GLP-1 Receptor Agonist Tirzepatide. **61**(7), 1057–1067. doi:10.1007/s40262-022-01140-3. 35674880