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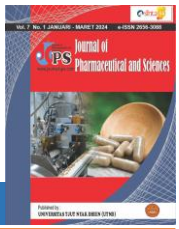

# Drug Interactions in Insulin Therapy Among Patients with Type 1 Diabetes Mellitus: A Retrospective Study

# Interaksi Obat dalam Terapi Insulin pada Pasien Diabetes Melitus Tipe 1: Studi Retrospektif

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**Abstract**

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disorder destroying pancreatic β-cells, leading to absolute insulin deficiency and hyperglycemia. Insulin remains the cornerstone of therapy; however, its use may be complicated by drug interactions that alter treatment effectiveness through pharmacodynamic or pharmacokinetic mechanisms. This study aimed to evaluate the prevalence and mechanisms of potential insulin drug interactions in patients with T1DM. A retrospective, cross-sectional study was conducted using a total sampling method. The study was conducted at Dr. M. Djamil General Hospital, Padang. The study population consisted of all hospitalized patients diagnosed with type 1 diabetes mellitus (T1DM) during the period 2019–2022. Patient characteristics, patterns of insulin therapy, and the occurrence of drug interactions were analyzed. The majority of patients were female (70%), and most were in the 0–18-year age group (83%). Insulin therapy was prescribed in 86.6% of cases. Potential drug–drug interactions were identified in 33.3% of hospitalized patients with type 1 diabetes mellitus, predominantly pharmacodynamic in nature. The basal–bolus insulin regimen constituted the most frequently prescribed therapeutic option among the patients. The Spearman correlation analysis indicated a statistically insignificant association between polypharmacy and the incidence of drug interactions. Systematic monitoring remains essential, and larger prospective studies are needed to confirm these findings.

***Keywords*: T1DM, Insulin, Drug Interactions, Pharmacodynamics, Pharmacokinetics.**

**Abstrak**

Diabetes Melitus Tipe 1 merupakan penyakit autoimun kronis yang menyebabkan destruksi sel β pankreas, sehingga menimbulkan defisiensi insulin absolut dan hiperglikemia. Insulin tetap menjadi terapi utama; namun, penggunaannya dapat dipersulit oleh adanya interaksi obat yang memengaruhi efektivitas terapi melalui mekanisme farmakodinamik maupun farmakokinetik. Penelitian ini bertujuan untuk mengevaluasi prevalensi dan mekanisme interaksi obat potensial dengan insulin pada pasien Diabetes Melitus Tipe 1. Penelitian dilakukan secara retrospektif dengan desain potong lintang menggunakan metode total sampling. Lokasi penelitian adalah di RSUP Dr. M. Djamil Padang dengan populasi seluruh pasien rawat inap yang didiagnosis Diabetes Melitus Tipe 1 pada periode 2019–2022. Karakteristik pasien, pola terapi insulin, serta kejadian interaksi obat dianalisis. Mayoritas pasien berjenis kelamin perempuan (70%) dan sebagian besar berada pada kelompok usia 0–18 tahun (83%). Terapi insulin diresepkan pada 86,6% kasus. Potensi interaksi obat ditemukan pada 33,3% pasien, dengan dominasi mekanisme farmakodinamik. Regimen insulin basal–bolus merupakan terapi yang paling banyak digunakan. Analisis korelasi Spearman menunjukkan tidak terdapat hubungan yang signifikan secara statistik antara metrik polifarmasi dengan insiden interaksi obat. Pemantauan sistematis tetap diperlukan, dan penelitian prospektif dengan jumlah sampel lebih besar disarankan untuk mengonfirmasi temuan ini.

***Kata Kunci*: T1DM, Insulin, Interaksi Obat, Farmakodinamika, Farmakokinetika.**

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## Introduction

Type 1 Diabetes Mellitus (T1DM), also referred to as Insulin-Dependent Diabetes Mellitus (IDDM), is a chronic autoimmune disorder characterized by persistent hyperglycemia resulting from the destruction of pancreatic β-cells [1,2]. Pancreatic β-cells play a central role in insulin production, which is essential for maintaining glucose homeostasis. At the onset of clinical symptoms, β-cell destruction has typically reached 80–95%, leaving patients with an absolute insulin deficiency [3,4]. T1DM most frequently occurs in children and adolescents and is predominantly associated with autoimmune mechanisms [1]. However, idiopathic forms of T1DM (type 1B) have also been described, which are characterized by insulin deficiency in the absence of autoimmune markers, and are often accompanied by an increased risk of diabetic ketoacidosis [2,5].

This heterogeneity in pathogenesis underscores the complexity of disease progression and poses significant challenges for long-term management. Given the lifelong requirement for insulin therapy, patients with T1DM remain vulnerable to various clinical complications and treatment-related issues. Understanding the mechanisms underlying β-cell destruction and their clinical implications is crucial for optimizing management strategies and improving patient outcomes.

Type 1 diabetes mellitus (T1DM) accounts for 5–10% of all diabetes cases worldwide (21–42 million individuals) and remains one of the most common chronic diseases in children. Recent advances in immunological therapy, such as teplizumab—recently approved by the U.S. FDA—have shown promise in delaying disease progression by preventing T-cell–mediated β-cell destruction, with reported adverse effects generally mild and transient [6]. Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Globally, the prevalence of diabetes continues to rise at an alarming rate. The International Diabetes Federation (IDF) reported that in 2021, approximately 537 million adults (20–79 years) worldwide were living with diabetes, with numbers projected to reach 643 million by 2030 and 783 million by 2045 [7].

These figures highlight the significant global burden of diabetes and the urgent need for effective management strategies. In Indonesia, the prevalence of diabetes has also shown an increasing trend. According to the National Basic Health Research (Riskesdas) survey in 2018, the prevalence of diabetes mellitus among individuals aged 15 years and older in West Sumatra increased by 1.5%. In contrast, in 2013, it was reported at 2.0%. Based on blood glucose examinations, the prevalence in this age group was 6.9% in 2013 and increased to 8.5% in 2018 [8]. Furthermore, the Indonesian Society of Endocrinology (PERKENI) reported a prevalence of 10.9% in 2018 [9]. According to the Indonesia Health Survey 2023, the prevalence of Type 1 Diabetes Mellitus (T1DM) in Indonesia was 16.9% among 14.935 individuals. In West Sumatra, the proportion was higher, at 22.9% of 226 individuals across all age groups. T1DM was most prevalent in the 5–14 years age group (55.7%), followed by the 15–24 years age group (29.3%) [10].

Treatment patterns in Indonesia indicate that the majority of patients (75%) rely on oral antidiabetic drugs (OAD), while 11% use a combination of OAD and insulin, and 9% receive no treatment [3]. Among patients prescribed insulin, 91% reported regular use, whereas 9% reported irregular use [3]. The main reasons for poor adherence include patients perceiving themselves as healthy, irregular medication use, reliance on traditional medicine, forgetfulness, side effects, financial constraints, and limited drug availability in healthcare facilities [9]. Insulin therapy remains the cornerstone of treatment in type 1 diabetes mellitus (T1DM) and is also frequently required in advanced type 2 diabetes mellitus (T2DM).



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However, the use of insulin may be complicated by potential drug interactions that can alter its therapeutic effectiveness through pharmacodynamic or pharmacokinetic mechanisms. While numerous studies have addressed the prevalence and management of diabetes in Indonesia, limited evidence exists regarding the prevalence, mechanisms, and clinical relevance of insulin-related drug interactions in patients with T1DM. This gap is critical, as unrecognized drug interactions may compromise glycemic control, increase the risk of complications, and affect treatment adherence. Drug interactions are defined as conditions in which the effect of a drug is altered by the concomitant use of another drug, food, or beverage, resulting in either desired or undesired outcomes [11].

A drug interaction is a modification in the pharmacological response of a drug when it is administered with other medicines, foods, herbal products, or specific chemical compounds. These alterations may occur through pharmacokinetic mechanisms, such as changes in absorption, distribution, metabolism, or excretion, or through pharmacodynamic mechanisms, involving modifications at the receptor level or within the same physiological system [12,13]. The clinical manifestations of drug interactions arise from these interactions and can significantly impact therapeutic outcomes. The severity of drug interactions is commonly classified as mild (not requiring therapy modification), moderate (requiring monitoring or dose adjustment), or severe (to be avoided due to the risk of toxicity or life-threatening events) [12,14].

Several studies in Indonesia have addressed this issue. Erlisa (2021) identified 13 drugs with potential interactions with insulin in outpatient prescriptions at Dr. Soedarso General Hospital, Pontianak, including nifedipine, aspirin, ramipril, lisinopril, clonidine, dexamethasone, and others. Aspirin was the most frequent interacting drug (29.90%), followed by ramipril (14.95%) and amitriptyline (11.21%). A total of 107 potential drug interaction events were documented, with pharmacodynamic interactions being the most dominant (59.45%) [15]. Meanwhile, Djahido (2020) reported that rapid-acting insulin was the most frequently prescribed regimen for patients with type 1 diabetes mellitus (65.39%), while combination insulin therapy was relatively rare (8.33%) [16].

There is a dearth of studies on insulin-related drug interactions in type 1 diabetes mellitus, particularly in Indonesia, which has contributed to the scarcity of data on their frequency and clinical impact. In Indonesia, the majority of existing research has predominantly focused on patients with type 2 diabetes mellitus, while studies specifically addressing type 1 diabetes mellitus remain limited. Given these gaps, this study aims to evaluate the characteristics and mechanisms of insulin drug interactions in hospitalized patients with T1DM, with particular emphasis on sociodemographic factors, daily medication burden, and insulin therapy patterns. To the best of our knowledge, this is among the first studies to address this issue in the Indonesian context, thereby contributing novel insights into the safe and effective management of insulin therapy in T1DM.

## Research Method Section

### Study Design

This study was conducted at Dr. M. Djamil General Hospital, Padang, Indonesia. A quantitative observational design with a cross-sectional framework was applied, using a retrospective review of electronic medical records. The study population included all inpatients diagnosed with type 1 diabetes mellitus (T1DM) between 2019 and 2022. Patients were enrolled based on predefined inclusion and exclusion criteria. The inclusion criteria were: (i) a confirmed diagnosis of T1DM (ICD-10 code: E10), (ii) receipt of insulin therapy in combination with other medications, and (iii) hospitalization during the period 2019–2022. Patients with incomplete medical records, particularly those lacking treatment data, were excluded. The independent variable was polypharmacy, and the dependent variable was the occurrence of potential drug–drug interactions (pDDIs). Identification of pDDIs was performed by cross-checking all prescribed medications using three established drug interaction resources: Drugs.com, Medscape Drug Interaction Checker, and Drug Interaction Facts. Interactions were classified by mechanism (pharmacokinetic vs. pharmacodynamic) and severity (mild, moderate, or severe) as defined in these databases. In cases of discrepancy, concordant classifications from at least two sources were adopted. When all three sources differed, the highest reported severity was selected, and the mechanism was determined based on the most pharmacologically plausible explanation supported by the literature. All discrepancies and final decisions were documented for transparency.


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**Ethical Clearance**

The Research Ethics Committee of Dr. M. Djamil General Hospital, Padang, West Sumatra, Indonesia, approved this study under ethical clearance number DP.04.03/D.XVI.XI/451/2024.

**Statistical Analysis**

Data were analyzed using descriptive statistics to summarize patient sociodemographic characteristics, patterns of insulin therapy, and the prevalence of pDDIs. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on data distribution. The association between the number of prescribed medications and the occurrence of pDDIs was evaluated using the Chi-square test. A p-value of <0.05 was considered statistically significant. Spearman's correlation was utilized to investigate the association between the extent of polypharmacy and the number of drug interaction events.

## Limitations of the study

This study has certain limitations: the identification of insulin–drug interactions was restricted to those documented in the literature and assessed retrospectively using data from hospitalized patients' medical records.

## Results and Discussion

**Sociodemographic Characteristics of Patients**

**Table 1.** Sociodemographic Characteristics of Patients

| Sociodemographic Characteristics | Number of Patients (n=30) | Percentage (%) |
|---|---|---|
| Age | | |
| Pediatric (0–18 years) | 25 | 83 |
| Adult (19–65 years) | 5 | 17 |
| Sex | | |
| Male | 9 | 30 |
| Female | 21 | 70 |

A total of 62 patients hospitalized with type 1 diabetes mellitus (T1DM) between 2019 and 2022 were initially identified. After eligibility screening, 30 patients met the inclusion criteria. They were included in the final analysis, while 32 patients were excluded due to incomplete medical records and insufficient treatment data, particularly regarding clinical outcomes. Analysis of demographic characteristics (Table 1) showed that most patients diagnosed with type 1 diabetes mellitus (T1DM) were children or adolescents. Among the 30 patients included, 25 (83%) were in the pediatric age group (0–18 years), while 5 (17%) were in the adult age group (19–65 years). Globally, the peak incidence of T1DM occurs between the ages of 5 and 14 years, with a progressive increase in cases among younger children in recent decades [17,18].

The predominance of pediatric cases in our findings underscores the need for early diagnosis and comprehensive management strategies to prevent acute complications such as diabetic ketoacidosis, which is a common reason for hospitalization in this population [19]. Regarding sex distribution, a higher proportion of females (70%) was observed than males (30%). Previous epidemiological studies have demonstrated variations in sex distribution across different populations. While some studies report a nearly equal incidence between males and females [20], others, particularly from Asian countries, have shown a female predominance in T1DM cases [21,22]. Genetic, hormonal, and environmental factors may contribute to this variation, although the underlying mechanisms remain incompletely understood.

Although nationwide epidemiological surveillance for T1DM in Indonesia remains inadequate, some descriptive reports are available. Pulungan et al. observed that T1DM prevalence in children has increased — from 3.88 per 100 million in 2000 to 28.19 per 100 million in 2010 — a sevenfold rise over a decade [23]. The Indonesian Pediatric Society (IDAI) recorded 1,220 pediatric T1DM cases in 2018 [24]. Moreover, the reality of underdiagnosis is emphasized, given the frequent initial presentation with DKA in Indonesian children [25]. Collectively, these findings suggest that women may be more susceptible to autoimmune-mediated diabetes



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or may exhibit greater engagement with health services, thereby increasing the likelihood of earlier detection and documentation. Overall, these sociodemographic characteristics highlight the vulnerability of pediatric patients, particularly females, to T1DM and its associated complications. This finding emphasizes the importance of tailored clinical management and the integration of multidisciplinary care, including pediatric endocrinologists, clinical pharmacists, and diabetes educators, to optimize outcomes in this high-risk group.

**Patterns of Insulin Therapy Use**

**Table 2.** Distribution of Basal–Bolus Insulin Therapy

| No | Type of Insulin Therapy | Insulin Name | Number of Patients (n) | Percentage (%) |
|---|---|---|---|---|
| 1 | Single | Levemir | 1 | 3.33 |
| | | Novorapid | 3 | 10 |
| 2 | Combination | Levemir + Novorapid | 26 | 86.67 |

In this study, insulin therapy was categorized into single (monotherapy) and combination regimens (Table 2). Single insulin therapy refers to the administration of either a basal insulin (e.g., Levemir) or a rapid-acting insulin (e.g., Novorapid) alone. This approach is often considered in older patients, those at high risk of hypoglycemia, or individuals in the early stages of diabetes treatment [26]. Although simpler to administer, monotherapy has significant limitations, particularly in managing complex glycemic fluctuations and controlling postprandial glucose excursions [27]. In this study, only a small proportion of patients (13.3%) received single insulin therapy. In contrast, the majority of patients (86.7%) were treated with a combination regimen consisting of basal insulin (Levemir) and rapid-acting insulin (Novorapid). This phenomenon is potentially attributed to the fact that the majority of Type 1 Diabetes patients admitted to Dr. M. Djamil Hospital, Padang, are in an advanced or severe State. This is consistent with the hospital's role as a Class A specialized referral center for West and Central Sumatra.

Basal bolus therapy has been widely recognized as the standard of care in type 1 diabetes mellitus (T1DM), as it more closely mimics physiological insulin secretion patterns and provides both long-term glycemic stability and flexibility in postprandial glucose control [28,29]. The combination of basal insulin with rapid-acting insulin allows for individualized adjustments, improving glycemic outcomes and reducing the risk of both hyperglycemia and hypoglycemia [30]. The predominance of the basal-bolus regimen observed at Dr. M. Djamil Hospital aligns with the current PERKENI guidelines; however, this approach simultaneously elevates the complexity of the therapeutic management. Consequently, the intensive regimen presents an increased potential for drug interactions if it is not accompanied by rigorous and constant monitoring.

The higher proportion of Novorapid use observed in this study may reflect its pharmacokinetic advantages, including a rapid onset and a shorter duration of action, making it particularly effective in controlling postprandial glucose surges [31]. Conversely, Levemir, as a long-acting basal insulin, ensures more stable glycemic control throughout the day and night, thereby preventing fasting hyperglycemia [32]. These findings are consistent with previous studies reporting increased use of insulin analogs in clinical practice. Previous study reported that insulin analogs, particularly basal–bolus regimens, were the most commonly prescribed therapies, highlighting their effectiveness and widespread clinical adoption [33, 34]. Overall, the predominance of basal–bolus combination therapy in this study underscores its clinical benefits and alignment with international treatment guidelines for T1DM management.

**Potential Insulin-Drug Interactions**

**Table 3.** Insulin–Drug Interaction Potential in Clinical Use

| Interaction Potential | Number of Patients (30) | Percentage (%) |
|---|---|---|
| Potential Interaction | 10 | 33.33 |
| No Potential Interaction | 20 | 66.67 |

Table 3 shows that this study's findings indicate that among 30 patients receiving insulin therapy, 10 (33.33%) were identified as having a potential risk of insulin-drug interactions, whereas 20 (66.67%) showed no such risk. This proportion is lower than that reported by Nurlaelah et al., who found that 52 patients (85.2%) were at risk of drug interactions in a hospital setting in Indonesia [35]. The difference in these percentages


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may be attributable to several factors, including differences in sample size, patient demographics, comorbidities, and the types of concomitant medications prescribed alongside insulin. The marked discrepancy in prevalence rates compared with those of Nurlaelah et al. (2015) may be attributed to variations in patient characteristics, such as disease severity and comorbidities, as well as to distinct prescribing policies implemented across the respective hospitals.

Identifying potential drug interactions in insulin therapy is essential, as such interactions may modify the pharmacological activity of concomitant drugs by either enhancing or diminishing their therapeutic effects, or by producing new, unintended adverse outcomes [36]. In certain cases, these interactions can have significant clinical implications. For instance, the concomitant use of insulin with sulfonylureas or other hypoglycemic agents can substantially increase the risk of hypoglycemia. In contrast, the use of insulin in combination with corticosteroids, thiazides, or beta-adrenergic agonists may reduce its effectiveness and lead to poor glycemic control [37,38].

Therefore, although the majority of patients in this study were not at risk of interactions, the presence of approximately one-third of patients with potential drug interactions warrants careful attention. These findings highlight the importance of active involvement by healthcare professionals, particularly clinical pharmacists, in monitoring pharmacotherapy, optimizing insulin regimens, and educating patients to minimize the risk of adverse clinical outcomes associated with insulin–drug interactions [39].

**Mechanism of Insulin Drug Interactions**

**Table 4.** Mechanism of Insulin Drug Interactions

| Mechanism of Interaction | Number of Cases (10) | Percentage (%) |
|---|---|---|
| Pharmacodynamic | 8 | 80 |
| Pharmacokinetic | 2 | 20 |
| Total | 10 | 100 |

Table 4 showed that 10 identified cases of potential insulin–drug interactions, most (8 cases; 80%) were pharmacodynamic, whereas the remaining 2 cases (20%) were pharmacokinetic. Pharmacodynamic interactions arise when one drug modifies the effect of another at its site of action, either enhancing or reducing its therapeutic effect. In insulin therapy, these interactions are particularly significant because they may result in clinically relevant outcomes, such as hypoglycemia when insulin is used alongside other glucose-lowering agents, or compromised glycemic control when insulin is used with hyperglycemia-inducing medications [40,37]. In contrast, pharmacokinetic interactions occur when the absorption, distribution, metabolism, or excretion of insulin or co-administered drugs is affected. Although these interactions were less common in this study (20%), they can still produce significant clinical effects, such as delayed onset of insulin action or changes in plasma drug levels, which may result in suboptimal glycemic control [41]. These results align with prior studies indicating that pharmacodynamic interactions represent the most frequent type of insulin-related drug interactions in both hospital and outpatient settings [42,38].

The prevalence of such interactions underscores the need for careful monitoring of blood glucose, particularly in patients receiving multiple medications that may affect insulin activity. Healthcare professionals, especially clinical pharmacists, are essential in detecting these interactions, optimizing treatment regimens, and providing patient education to reduce the risk of adverse effects [43]. The majority of identified interactions were pharmacodynamic, including combinations such as insulin with dexamethasone, candesartan, ramipril, and glibenclamide. Pharmacodynamic interactions occur when one drug modifies the effect of another at its site of action, either enhancing or diminishing therapeutic outcomes [36,37]. In insulin therapy, these interactions are clinically significant, as they may lead to hypoglycemia when combined with glucose-lowering agents or reduced glycemic control when administered alongside hyperglycemia-inducing drugs [38].

The co-administration of insulin and dexamethasone results in a clinically relevant interaction due to glucocorticoids' metabolic effects. Dexamethasone reduces peripheral insulin sensitivity and promotes hepatic gluconeogenesis, leading to steroid-induced hyperglycemia. This pharmacodynamic interaction often necessitates an increase in insulin requirements to maintain optimal glycemic control during corticosteroid therapy [39]. This interaction results in Glucocorticoid-Induced Hyperglycemia (GIH), a common metabolic complication of corticosteroid therapy. The mechanism is multi-factorial and affects multiple organ systems



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essential for glucose homeostasis. Dexamethasone directly impairs the insulin signaling cascade post-receptor (after insulin binds to its receptor). Specifically, glucocorticoids inhibit the translocation of Glucose Transporter 4 (GLUT4) from the cell cytoplasm to the plasma membrane. This blockade reduces the capacity of muscle and fat cells to take up glucose from the bloodstream, thereby promoting peripheral insulin resistance [46].

In hospitalized patients with type 1 diabetes mellitus, this interaction underscores the need for intensive monitoring. Frequent blood glucose assessments—ideally 4 to 6 times per day or according to individualized clinical targets—are recommended to identify hyperglycemic excursions [38] promptly. Adjustments to insulin regimens, including temporary dose escalation, may be required throughout the course of dexamethasone therapy. Moreover, careful consideration must be given during steroid tapering or discontinuation, as insulin needs may decrease, predisposing patients to hypoglycemia if doses are not appropriately reduced [38,39]. Effective management also relies on interprofessional collaboration. Pharmacists, physicians, and nursing staff should work together to ensure dynamic dose titration, patient safety, and prevention of acute complications associated with fluctuating glycemic levels. Such coordinated care is essential in optimizing outcomes for patients receiving both insulin and dexamethasone.

The interaction between Candesartan and Insulin is a pharmacodynamic interaction characterized by Candesartan's insulin-sensitizing effects. Unlike the interaction with Dexamethasone, this interaction is generally beneficial, as Candesartan augments the activity of endogenous and exogenous insulin, potentially increasing the risk of hypoglycemia in patients concurrently receiving insulin therapy. Candesartan, by selectively blocking the Angiotensin II Type 1 receptor, improves glucose metabolism through mechanisms that are partly independent of its blood pressure-lowering effects. This improvement in insulin sensitivity is the mechanism that allows Angiotensin Receptor Blockers (ARBs), including Candesartan, to be associated with a reduced incidence of new-onset Type 2 Diabetes [47].

Pharmacokinetic interactions, though less frequent, were also noted, including combinations of insulin with captopril, metformin, or other oral antidiabetic agents. These interactions can modify insulin absorption, distribution, metabolism, or excretion, potentially increasing the risk of hypoglycemia or altering therapeutic efficacy [48,49]. For example, concomitant use of insulin with ACE inhibitors or angiotensin receptor blockers, such as ramipril or candesartan, can potentiate insulin effects and elevate the risk of hypoglycemia [50]. Ramipril, like other ACE inhibitors and ARBs (such as Candesartan), is associated with metabolic effects that enhance insulin action. This interaction is primarily mediated through the inhibition of the Renin-Angiotensin-Aldosterone System (RAAS) and the modulation of tissue kinins. However, in patients already dependent on Insulin therapy (such as those with Type 1 Diabetes or insulin-dependent Type 2 Diabetes), the enhanced insulin sensitivity poses a risk of Hypoglycemia, which is the primary clinical concern. The increased susceptibility to hypoglycemia, particularly when Ramipril therapy is initiated or the dose is escalated, is a key concern. Patients initiating Ramipril therapy often require a downward adjustment of their insulin dose to prevent symptomatic hypoglycemia and maintain optimal glycemic control [57].

Similarly, co-administration of insulin with metformin or glibenclamide may produce synergistic glycemic control but necessitates careful dose adjustment to prevent adverse events [51]. These findings align with previous research indicating that pharmacodynamic interactions are the most prevalent type of insulin-related drug interactions in both inpatient and outpatient settings (1,2,5). The predominance of pharmacodynamic interactions underscores the critical role of healthcare professionals, particularly clinical pharmacists, in monitoring therapy, identifying potential interactions, adjusting insulin regimens, and educating patients to reduce adverse outcomes [52]. Although the concurrent use of exogenous Insulin and the sulfonylurea Glibenclamide commonly increases the risk of synergistic hypoglycemia in patients with Type 2 Diabetes Mellitus, an exceptional clinical context arises in pediatrics, specifically in children with Permanent Neonatal Diabetes Mellitus linked to gain-of-function mutations in KATP channel genes (e.g., KCNJ11 or ABCC8). In these specific genetically confirmed cases, Glibenclamide serves as the definitive monotherapy. Its mechanism of action directly reverses channel dysfunction, effectively restoring endogenous insulin secretion and facilitating the successful, often complete cessation of exogenous insulin administration. Hence, the traditional drug 'interaction' in the sense of additive hypoglycemic risk is rendered irrelevant, as Glibenclamide functions as a replacement rather than an augmentation to the insulin regimen, contributing to both enhanced glycemic control and substantial therapeutic simplification [58].


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**Table 5.** Correlation Analysis of Polypharmacy and Potential Drug–Drug Interactions Using Spearman's Rho

| Correlations | | | | |
|---|---|---|---|---|
| | | | Polypharmacy | Potential Drug-Drug Interactions |
| Spearman's rho | Polypharmacy | Correlation Coefficient | 1.000 | .320 |
| | | Sig. (2-tailed) | . | .085 |
| | | N | 30 | 30 |
| | Potential Drug-Drug Interactions | Correlation Coefficient | .320 | 1.000 |
| | | Sig. (2-tailed) | .085 | . |
| | | N | 30 | 30 |

Spearman's correlation analysis revealed no statistically significant association between polypharmacy and the incidence of drug interactions ($r_s$ 0.320, p = 0.085). This finding, further supported by the higher average number of medications in the group without interactions, suggests that qualitative factors (drug type) may be more influential than quantitative factors (number of drugs) in precipitating drug interactions in this population. The lack of statistical significance may be partly due to the relatively small sample size (n = 30), which likely reduced the power to detect a meaningful association. In this study, 10 patients (33.3%) experienced potential drug interactions, while 20 patients (66.7%) did not. Interestingly, the average number of drugs prescribed per day was slightly higher in patients without potential interactions (3.70 ± 0.470) compared to those with potential interactions (3.40 ± 1.075). This finding contrasts with the general assumption that an increasing number of medications necessarily results in a higher probability of drug–drug interactions. Previous studies have consistently shown that polypharmacy represents a significant risk factor for drug interactions, particularly in patients with chronic illnesses requiring long-term therapy, including those with diabetes mellitus [53,54].

Nevertheless, our findings suggest that the total number of prescribed drugs does not solely determine the occurrence of potential drug interactions. Instead, the risk appears to be more strongly influenced by the specific pharmacodynamic and pharmacokinetic properties of the drugs involved [55]. This observation is in line with prior evidence highlighting that drug class, mechanism of action, and metabolic pathways may play a more critical role than polypharmacy alone in determining the likelihood and severity of drug interactions [56]. These results underscore the importance of evaluating not only the quantity but also the type and clinical context of medications in hospitalized T1DM patients. Clinical pharmacists, therefore, play a pivotal role in monitoring drug regimens, identifying clinically relevant interactions, and ensuring therapeutic safety.

Future studies with larger sample sizes and prospective designs are warranted to confirm these findings and further elucidate the clinical implications of drug–drug interactions in T1DM management. The interpretation and generalization of the results must acknowledge several limitations. Primarily, the retrospective study design introduces inherent information bias, as the accuracy and integrity of the input variables relied strictly on the quality and completeness of the electronic medical record documentation. Furthermore, the analysis focused exclusively on potential drug-drug interactions (DDIs) identified via literature review; without correlated clinical outcome data (e.g., incidence of symptomatic hypoglycemia or hyperglycemia), we cannot definitively conclude that these potential DDIs actually manifested clinically or resulted in patient harm, thereby limiting the practical clinical significance of the findings. Finally, the relatively small sample size (n=30) significantly constrains the statistical power and the generalizability of the findings, requiring caution when extrapolating these results to the broader population of Type 1 Diabetes Mellitus patients.

## Conclusions

This study identified a prevalence of 33.3% for potential drug–drug interactions (pDDIs) among hospitalized patients with type 1 diabetes mellitus, with the majority (80%) categorized as pharmacodynamic. The basal–bolus insulin regimen was the most frequently prescribed therapeutic pattern, reflecting standard practice in this patient population. Although polypharmacy is often regarded as a key determinant of interaction risk, the Spearman correlation analysis indicated a statistically insignificant association between


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polypharmacy and the incidence of drug interactions ($r_s$ = 0.320, p = 0.085). This suggests that the type and pharmacological properties of drugs may be more influential than medication count alone in determining the likelihood of interactions. These findings highlight the importance of systematic monitoring and active clinical pharmacist involvement in therapy evaluation to mitigate risks and optimize outcomes. Future prospective studies with larger cohorts are warranted to confirm these prevalence estimates, further explore the role of polypharmacy, and evaluate the real-world clinical consequences of insulin-related drug interactions in patients with type 1 diabetes mellitus.

## Conflict of Interest

All authors declare no conflict of interest in this study.

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