RESEARCH PAPER

Association of Polypharmacy with Renal and Hepatic Biochemical Abnormalities in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Polypharmacy, commonly defined as the concurrent use of five or more medications, is increasingly prevalent among patients with type 2 diabetes mellitus (T2DM) because of the progressive nature of the disease and the high burden of comorbidities. While polypharmacy is often necessary to achieve multifaceted therapeutic goals, accumulating evidence suggests that it may contribute to renal and hepatic biochemical derangements through drug–drug interactions, cumulative nephrotoxic and hepatotoxic burden, and altered pharmacokinetics.

Objective: To evaluate the association between polypharmacy and renal and hepatic biochemical abnormalities in patients with T2DM.

Methods: A cross-sectional observational study was conducted by TRR College of Pharmacy, Hyderabad, over a four-month period (5 April 2026 to 5 August 2026) among 48 patients with T2DM attending its affiliated tertiary care teaching hospital. Patients were stratified into polypharmacy (≥5 medications, n=24) and non-polypharmacy (<5 medications, n=24) groups. Renal function was assessed using serum creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (UACR). Hepatic function was evaluated using serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin. Data were analysed using SPSS version 26.0, with $p<0.05$ considered statistically significant.

Results: The mean age of participants was 58.4 ± 9.6 years, with 56.3% male. The polypharmacy group demonstrated significantly higher serum creatinine (1.42 ± 0.38 vs. 1.08 ± 0.24 mg/dL, $p<0.001$), BUN (22.6 ± 6.8 vs. 16.4 ± 4.2 mg/dL, $p<0.001$), and UACR (86.4 ± 32.6 vs. 48.2 ± 21.4 mg/g, $p<0.001$), with significantly lower eGFR (62.8 ± 18.4 vs. 82.6 ± 15.2 mL/min/1.73 m², $p<0.001$). Hepatic parameters were also significantly elevated in the polypharmacy group: AST (42.6 ± 12.8 vs. 28.4 ± 8.6 U/L, $p<0.001$), ALT (48.2 ± 15.4 vs. 31.6 ± 10.2 U/L, $p<0.001$), and ALP (118.6 ± 28.4 vs. 92.4 ± 22.6 U/L, $p<0.001$). The number of medications demonstrated significant positive correlations with serum creatinine ($r=0.642$, $p<0.001$), UACR ($r=0.586$, $p<0.001$), AST ($r=0.524$, $p<0.001$), and ALT ($r=0.548$, $p<0.001$), and a significant negative correlation with eGFR ($r=-0.612$, $p<0.001$). The prevalence of renal abnormalities (eGFR<60 mL/min/1.73 m²) was 41.7% in the polypharmacy group versus 12.5% in the non-polypharmacy group ($p=0.024$), while hepatic abnormalities (ALT>40 U/L) were present in 45.8% versus 16.7%, respectively ($p=0.031$).

Conclusion: Polypharmacy was significantly associated with renal and hepatic biochemical abnormalities in patients with T2DM. Although the cross-sectional design and between-group differences in diabetes duration and comorbidity burden preclude causal inference, these findings support regular biochemical monitoring and structured medication reviews in this population to limit organ-specific harm and optimise therapeutic outcomes.

Keywords: Polypharmacy; Type 2 diabetes mellitus; Renal function; Hepatic function; Biochemical abnormalities; Drug safety

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a formidable global health challenge, with an estimated 589 million adults aged 20–79 years affected worldwide, a figure projected to rise to 853 million by 2050 [1]. India bears a disproportionate burden of this epidemic, with a national diabetes prevalence of 11.4% (approximately 101 million adults) and substantial regional heterogeneity [2]. The progressive

nature of T2DM necessitates escalating pharmacological intervention over time, and the coexistence of hypertension, dyslipidaemia, cardiovascular disease, and chronic kidney disease (CKD) further compounds medication burden, rendering polypharmacy an almost inevitable consequence of comprehensive diabetes management [3].

Polypharmacy, most commonly defined as the concurrent use of five or more medications [4], has historically carried a negative connotation because of its association with adverse drug events, drug–drug interactions, medication non-adherence, and increased healthcare costs [3,4]. However, contemporary discourse distinguishes between appropriate polypharmacy where multiple evidence-based therapies are required to achieve multifaceted health goals and inappropriate polypharmacy, where the risk of harm outweighs clinical benefit [3]. In T2DM, the absence of polypharmacy may, in fact, signify under-prescribing or missed opportunities for essential cardiorenal and vascular risk reduction [3]. Nevertheless, the cumulative nephrotoxic and hepatotoxic burden of multiple concomitant medications remains a legitimate concern that warrants systematic investigation [5,6].

The kidneys and liver are the principal organs responsible for drug metabolism and elimination, rendering them particularly vulnerable to drug-related injury in the setting of polypharmacy [6,7]. Renal function decline in T2DM is driven by hyperglycaemia-induced oxidative stress, inflammation, and fibrosis, and may be exacerbated by nephrotoxic medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), certain antihypertensives, and contrast agents [7]. Similarly, the liver already affected by metabolic dysfunction-associated steatotic liver disease (MASLD) in more than half of patients with T2DM [8] may sustain further injury from potentially hepatotoxic drugs, including certain oral hypoglycaemic agents, statins, and antibiotics [6]. Drug-induced liver injury (DILI) is a significant concern; a recent meta-analysis found diabetes mellitus to be associated with a 30% higher risk of DILI among older adults (OR 1.30, 95% CI 1.10–1.54) [6].

Despite the biological plausibility and clinical importance of this association, real-world evidence examining the relationship between polypharmacy and renal and hepatic biochemical abnormalities in T2DM remains scarce, particularly in the Indian context. Existing studies have predominantly focused on older adults and on the prevalence of polypharmacy and potentially inappropriate medications rather than on organ function [9,10], although polypharmacy has been linked to poorer renal outcomes in patients treated with sodium–glucose cotransporter 2 (SGLT2) inhibitors [5]. This knowledge gap is particularly consequential for India, where polypharmacy is common among older adults [11] and a large proportion of diabetes remains undiagnosed [2]. The present study was therefore undertaken to evaluate the association of polypharmacy with renal and hepatic biochemical abnormalities in patients with T2DM attending a tertiary care setting in India.

OBJECTIVE

The primary objective of this study was to evaluate the association between polypharmacy (defined as the concurrent use of five or more medications) and renal biochemical abnormalities in patients with T2DM. Renal function was assessed using serum creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), and urine albumin-to-creatinine ratio (UACR). The secondary objective was to assess the association between polypharmacy and hepatic biochemical abnormalities, evaluated through serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin levels. Additionally, the study sought to determine the prevalence of renal and hepatic biochemical abnormalities in patients with polypharmacy compared to those without polypharmacy, and to examine the correlation between the number of prescribed medications and the magnitude of biochemical derangements in this population.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional observational study was conducted by TRR College of Pharmacy, Hyderabad, over a four-month period from 5 April 2026 to 5 August 2026. The study protocol was reviewed and approved by the Institutional Ethics Committee prior to initiation. The study population comprised patients with T2DM attending the outpatient department and medicine ward of the affiliated tertiary care teaching hospital. A total of 48 patients meeting the eligibility criteria were enrolled using a consecutive sampling technique. The sample size was determined on the basis of feasibility within the study period. All participants provided written informed consent prior to enrolment, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Inclusion criteria: (i) Patients aged ≥18 years with a confirmed diagnosis of T2DM according to the American Diabetes Association criteria (fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, HbA1c ≥6.5%, or random plasma glucose ≥200 mg/dL with classic symptoms of hyperglycaemia) [12], (ii)

patients with a documented history of T2DM for at least one year, (iii) patients on stable medication regimens for at least three months prior to enrolment, (iv) patients with complete medical records including recent biochemical investigations, and (v) patients who provided informed consent.

Exclusion criteria: (i) Patients with type 1 diabetes mellitus or secondary diabetes, (ii) patients with pre-existing chronic kidney disease stage 4 or 5 (eGFR <30 mL/min/1.73 m²) or on renal replacement therapy, (iii) patients with pre-existing chronic liver disease, cirrhosis, or documented hepatitis B or C infection, (iv) patients with acute illness, sepsis, or hospitalisation within the preceding three months, (v) patients with malignancy or receiving chemotherapy, (vi) pregnant or lactating women, and (vii) patients on medications with established hepatotoxic or nephrotoxic potential for non-diabetic indications (e.g., antitubercular therapy, immunosuppressants).

Data Collection Procedure

Data were collected using a structured case record form specifically designed for this study. Demographic information including age, sex, duration of diabetes, and body mass index (BMI) was recorded. Detailed medication histories were obtained by reviewing prescription records, patient interviews, and medication diaries. The total number of medications was recorded, including all prescription medications, over-the-counter drugs, and herbal supplements. Polypharmacy was defined as the concurrent use of five or more medications, consistent with the most widely accepted numerical definition in the literature [3,4]. Patients were stratified into two groups: the polypharmacy group (≥5 medications, n=24) and the non-polypharmacy group (<5 medications, n=24).

Venous blood samples (5 mL) were collected after an overnight fast of at least 8 hours. Serum was separated by centrifugation at 3000 rpm for 10 minutes and analysed using standard laboratory techniques. Renal function parameters included serum creatinine (measured by Jaffe alkaline picrate method), BUN (measured by urease-GLDH method), eGFR (calculated using the CKD-EPI equation), and UACR (measured by immunoturbidimetric method on spot urine samples). Hepatic function parameters included serum AST and ALT (measured by IFCC method), ALP (measured by p-nitrophenyl phosphate method), and total bilirubin (measured by diazo method). All biochemical analyses were performed in a single accredited laboratory to ensure consistency and minimise inter-assay variability. Glycaemic control was assessed using HbA1c (measured by HPLC method).

Statistical Data Analysis

Data were analysed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). The normality of distribution of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean ± standard deviation (SD) and compared between groups using the independent samples t-test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test, or Fisher's exact test when any expected cell count was less than 5. Pearson's correlation coefficient was used to examine the relationship between the number of medications and biochemical parameters. A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 48 patients with T2DM were enrolled, with 24 patients in the polypharmacy group (≥5 medications) and 24 patients in the non-polypharmacy group (<5 medications). The baseline demographic and clinical characteristics of the study participants are presented in Table 1. The mean age of the overall cohort was 58.4 ± 9.6 years, with a male predominance (56.3%). There were no statistically significant differences between the groups with respect to age (p=0.321), sex distribution (p=0.771), or BMI (p=0.305). However, patients in the polypharmacy group had a significantly longer duration of diabetes (11.8 ± 5.4 vs. 7.2 ± 4.1 years, p=0.002), higher HbA1c (8.6 ± 1.4 vs. 7.8 ± 1.2%, p=0.038), and a significantly higher prevalence of comorbidities including hypertension (83.3% vs. 45.8%, p=0.008), dyslipidaemia (75.0% vs. 37.5%, p=0.009), and cardiovascular disease (41.7% vs. 12.5%, p=0.024). Insulin use was also more frequent in the polypharmacy group (33.3% vs. 8.3%, p=0.031). The mean number of medications was 7.4 ± 1.8 in the polypharmacy group and 3.2 ± 0.9 in the non-polypharmacy group (p<0.001). Metformin was the most commonly prescribed antidiabetic agent (81.3%), followed by sulfonylureas (58.3%) and DPP-4 inhibitors (31.3%).

The renal biochemical parameters are summarised in Table 2. Patients in the polypharmacy group demonstrated significantly higher serum creatinine (1.42 ± 0.38 vs. 1.08 ± 0.24 mg/dL, p<0.001), BUN (22.6 ± 6.8 vs. 16.4 ± 4.2 mg/dL, p<0.001), and UACR (86.4 ± 32.6 vs. 48.2 ± 21.4 mg/g, p<0.001) compared to the non-polypharmacy group. Conversely, eGFR was significantly lower in the polypharmacy group (62.8 ± 18.4 vs. 82.6 ± 15.2 mL/min/1.73 m², p<0.001). The prevalence of renal abnormalities, defined as eGFR <60 mL/min/1.73 m², was 41.7% in the polypharmacy group compared to 12.5% in the non-polypharmacy group (p=0.024). Similarly, the prevalence of albuminuria (UACR >30 mg/g) was 62.5% versus 29.2%, respectively (p=0.019). The hepatic biochemical parameters are presented in Table 3. The polypharmacy group exhibited significantly

higher serum AST (42.6 ± 12.8 vs. 28.4 ± 8.6 U/L, p<0.001), ALT (48.2 ± 15.4 vs. 31.6 ± 10.2 U/L, p<0.001), ALP (118.6 ± 28.4 vs. 92.4 ± 22.6 U/L, p<0.001), and total bilirubin (0.92 ± 0.28 vs. 0.68 ± 0.18 mg/dL, p=0.001) compared to the non-polypharmacy group. The prevalence of hepatic abnormalities, defined as ALT >40 U/L, was 45.8% in the polypharmacy group versus 16.7% in the non-polypharmacy group (p=0.031), while the prevalence of AST >40 U/L was 41.7% versus 12.5%, respectively (p=0.024).

The correlation between the number of medications and biochemical parameters is presented in Table 4. A significant positive correlation was observed between the number of medications and serum creatinine (r=0.642, p<0.001), BUN (r=0.528, p<0.001), UACR (r=0.586, p<0.001), AST (r=0.524, p<0.001), ALT (r=0.548, p<0.001), ALP (r=0.462, p=0.001), and total bilirubin (r=0.398, p=0.005). A significant negative correlation was observed between the number of medications and eGFR (r=−0.612, p<0.001). Table 5 summarises the prevalence of renal and hepatic biochemical abnormalities across both groups. The polypharmacy group consistently demonstrated higher rates of all assessed abnormalities, with statistically significant differences for low eGFR, albuminuria, elevated AST, elevated ALT, and elevated ALP, whereas the difference in hyperbilirubinaemia (>1.2 mg/dL) was not statistically significant (16.7% vs. 4.2%, p=0.348).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Characteristic	Polypharmacy Group (n=24)	Non-Polypharmacy Group (n=24)	p-value
Age (years), mean ± SD	59.8 ± 9.2	57.0 ± 10.1	0.321
Male sex, n (%)	14 (58.3%)	13 (54.2%)	0.771
BMI (kg/m²), mean ± SD	27.8 ± 4.2	26.6 ± 3.8	0.305
Duration of diabetes (years), mean ± SD	11.8 ± 5.4	7.2 ± 4.1	0.002 *
HbA1c (%), mean ± SD	8.6 ± 1.4	7.8 ± 1.2	0.038 *
Hypertension, n (%)	20 (83.3%)	11 (45.8%)	0.008 *
Dyslipidaemia, n (%)	18 (75.0%)	9 (37.5%)	0.009 *
Cardiovascular disease, n (%)	10 (41.7%)	3 (12.5%)	0.024 *
Number of medications, mean ± SD	7.4 ± 1.8	3.2 ± 0.9	<0.001*
Metformin use, n (%)	20 (83.3%)	19 (79.2%)	1.000 †
Sulfonylurea use, n (%)	16 (66.7%)	12 (50.0%)	0.245
DPP-4 inhibitor use, n (%)	9 (37.5%)	6 (25.0%)	0.354
SGLT2 inhibitor use, n (%)	6 (25.0%)	4 (16.7%)	0.480
Insulin use, n (%)	8 (33.3%)	2 (8.3%)	0.031 *

*Statistically significant (p<0.05); †Fisher's exact test. Continuous variables compared by independent samples t-test and categorical variables by chi-square test unless otherwise indicated. BMI: body mass index; HbA1c: glycated haemoglobin; DPP-4: dipeptidyl peptidase-4; SGLT2: sodium–glucose cotransporter 2.

Table 2: Renal Biochemical Parameters in Polypharmacy and Non-Polypharmacy Groups

Parameter	Polypharmacy Group (n=24)	Non-Polypharmacy Group (n=24)	p-value
Serum creatinine (mg/dL), mean ± SD	1.42 ± 0.38	1.08 ± 0.24	<0.001*
Blood urea nitrogen (mg/dL), mean ± SD	22.6 ± 6.8	16.4 ± 4.2	<0.001*
eGFR (mL/min/1.73 m²), mean ± SD	62.8 ± 18.4	82.6 ± 15.2	<0.001*
UACR (mg/g), mean ± SD	86.4 ± 32.6	48.2 ± 21.4	<0.001*
eGFR <60 mL/min/1.73 m², n (%)	10 (41.7%)	3 (12.5%)	0.024 *
UACR >30 mg/g, n (%)	15 (62.5%)	7 (29.2%)	0.019 *

*Statistically significant (p<0.05); eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio

Table 3: Hepatic Biochemical Parameters in Polypharmacy and Non-Polypharmacy Groups

Parameter	Polypharmacy Group (n=24)	Non-Polypharmacy Group (n=24)	p-value
AST (U/L), mean ± SD	42.6 ± 12.8	28.4 ± 8.6	<0.001*
ALT (U/L), mean ± SD	48.2 ± 15.4	31.6 ± 10.2	<0.001*
ALP (U/L), mean ± SD	118.6 ± 28.4	92.4 ± 22.6	<0.001*
Total bilirubin (mg/dL), mean ± SD	0.92 ± 0.28	0.68 ± 0.18	0.001*
AST >40 U/L, n (%)	10 (41.7%)	3 (12.5%)	0.024*
ALT >40 U/L, n (%)	11 (45.8%)	4 (16.7%)	0.031*
ALP >120 U/L, n (%)	8 (33.3%)	2 (8.3%)	0.031*

*Statistically significant (p<0.05); AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase

Table 4: Correlation Between Number of Medications and Biochemical Parameters

Parameter	Pearson's r	p-value
Serum creatinine	0.642	<0.001*
Blood urea nitrogen	0.528	<0.001*
eGFR	−0.612	<0.001*
UACR	0.586	<0.001*
AST	0.524	<0.001*
ALT	0.548	<0.001*
ALP	0.462	0.001*
Total bilirubin	0.398	0.005*

*Statistically significant (p<0.05)

Table 5: Prevalence of Renal and Hepatic Biochemical Abnormalities

Abnormality	Polypharmacy Group (n=24)	Non-Polypharmacy Group (n=24)	p-value
Low eGFR (<60 mL/min/1.73 m²)	10 (41.7%)	3 (12.5%)	0.024*
Albuminuria (UACR >30 mg/g)	15 (62.5%)	7 (29.2%)	0.019*
Elevated AST (>40 U/L)	10 (41.7%)	3 (12.5%)	0.024*
Elevated ALT (>40 U/L)	11 (45.8%)	4 (16.7%)	0.031*
Elevated ALP (>120 U/L)	8 (33.3%)	2 (8.3%)	0.031*
Hyperbilirubinaemia (>1.2 mg/dL)	4 (16.7%)	1 (4.2%)	0.348†

*Statistically significant (p<0.05); †Fisher's exact test. eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase.

DISCUSSION

The present study demonstrates a significant association between polypharmacy and both renal and hepatic biochemical abnormalities in patients with T2DM. Patients on five or more medications exhibited significantly higher serum creatinine, BUN, UACR, AST, ALT, ALP, and total bilirubin levels, along with significantly lower eGFR, compared with those on fewer medications. These findings are consistent with the growing body of evidence implicating polypharmacy as a potentially modifiable contributor to organ-specific harm in diabetes [3,5,6]. Half of our cohort (50%) met the definition of polypharmacy, which is comparable to the pooled prevalence of 49% reported among older adults in India [11]. The polypharmacy group also carried a heavier disease burden, with hypertension, dyslipidaemia, and cardiovascular disease being significantly more common, together with a longer duration of diabetes and poorer glycaemic control.

Our renal findings are in line with those of Nisa et al., who reported that among patients with diabetic nephropathy, polypharmacy (OR 1.83, 95% CI 1.42–2.36) and lower eGFR (OR 1.67, 95% CI 1.28–2.19) were significantly associated with the prescription of potentially inappropriate medications [10]. The mechanisms underlying polypharmacy-associated renal injury are multifactorial. First, the cumulative nephrotoxic burden of multiple medications including NSAIDs and certain antihypertensives can exacerbate

hyperglycaemia-induced renal injury through haemodynamic alterations and direct tubular toxicity [7]. Second, drug–drug interactions may impair renal clearance of antidiabetic agents; for instance, trimethoprim can inhibit the renal elimination of metformin and increase metformin exposure by 37%, potentiating the risk of lactic acidosis in the setting of reduced renal function [13]. Third, the prescribing cascade where an adverse effect of one medication is misinterpreted as a new condition and treated with another medication may further compound renal risk. The significant negative correlation between the number of medications and eGFR ($r=-0.612$) suggests a graded relationship between medication burden and renal function. However, because patients with declining renal function typically receive additional medications for associated comorbidities, the direction of this association cannot be established from the present data.

The hepatic findings of our study add to the limited body of evidence examining polypharmacy-associated hepatic abnormalities in T2DM. The significantly elevated AST, ALT, ALP, and bilirubin levels in the polypharmacy group are consistent with the known hepatotoxic potential of medications commonly prescribed in this population, including sulfonylureas, statins, and certain antibiotics [6,14]. A recent systematic review and meta-analysis by Fan et al. reported that diabetes mellitus was associated with a 30% increased risk of DILI among older adults (OR 1.30, 95% CI 1.10–1.54) and highlighted polypharmacy as a contributor to synergistic hepatotoxicity [6]. Our finding of significant positive correlations between the number of medications and ALT ($r=0.548$) and AST ($r=0.524$) is consistent with this hypothesis. The liver, already affected by MASLD in a substantial proportion of patients with T2DM [8], may be particularly vulnerable to the cumulative burden of multiple medications; conversely, because MASLD itself raises aminotransferase levels and was not assessed in this study, it may partly account for the observed differences. Interestingly, a recent study by Khudhur et al. demonstrated that sulfonylurea use was associated with significantly higher ALT, AST, ALP, and bilirubin levels compared with metformin, DPP-4 inhibitors, and SGLT2 inhibitors, suggesting that the choice of antidiabetic agent may modulate hepatic risk [14]. This is clinically relevant, as our polypharmacy group had a higher prevalence of sulfonylurea use (66.7% vs. 50.0%), although this difference did not reach statistical significance.

The clinical implications of our findings are substantial. First, they underscore the need for regular biochemical monitoring including renal function tests and liver function tests in patients with T2DM on polypharmacy, in line with current guidelines [12]. Second, they highlight the need for structured medication reviews and deprescribing initiatives, particularly in patients with multiple comorbidities, to identify and discontinue potentially inappropriate or redundant medications [3,10]. Third, they suggest that the choice of antidiabetic agents should be individualised based on renal and hepatic function, with preferential use of agents with favourable organ safety profiles, such as SGLT2 inhibitors and DPP-4 inhibitors, in patients with compromised organ function [12,14]. Fourth, the graded correlations between the number of medications and biochemical abnormalities reinforce the importance of minimising medication burden where clinically feasible. Finally, our findings add to the evidence supporting the distinction between appropriate and inappropriate polypharmacy, and the need for clinical context-based medication optimisation beyond numerical thresholds [3,9].

LIMITATIONS OF THE STUDY

This study has several limitations that warrant consideration. First, the cross-sectional design precludes establishment of causality between polypharmacy and renal and hepatic biochemical abnormalities; longitudinal studies are needed to confirm temporal relationships and assess the impact of medication changes over time. Second, the relatively small sample size (n=48) limits the generalisability of the findings and may have resulted in insufficient statistical power to detect small but clinically meaningful differences. Third, the study was conducted at a single centre, which may introduce selection bias and limit external validity. Fourth, medication adherence was not objectively assessed, and the actual consumption of prescribed medications may differ from prescription records. Fifth, and most importantly, the polypharmacy group had a longer duration of diabetes, poorer glycaemic control, and a higher prevalence of hypertension, dyslipidaemia, cardiovascular disease, and insulin use; because no multivariable analysis was performed, the observed differences may partly reflect greater disease severity rather than medication burden per se (confounding by indication). Other potential confounders, including duration of individual medication use, cumulative drug doses, alcohol consumption, smoking status, hepatic steatosis, and genetic polymorphisms affecting drug metabolism, were also not accounted for. Sixth, multiple comparisons were performed without adjustment, so findings with p-values between 0.01 and 0.05 should be interpreted with caution. Seventh, the definition of polypharmacy as ≥5 medications, while widely accepted, does not account for the appropriateness of individual medications or the duration of therapy. Eighth, biochemical parameters were assessed at a single time point and may not reflect

long-term trends. Finally, the study population was relatively young (mean age 58.4 years) compared with typical polypharmacy cohorts, which may limit comparability with studies in older adults.

CONCLUSION

In conclusion, this study demonstrates a significant association between polypharmacy and renal and hepatic biochemical abnormalities in patients with T2DM. Patients on five or more medications exhibited significantly higher serum creatinine, BUN, UACR, AST, ALT, ALP, and total bilirubin levels, along with significantly lower eGFR, compared with those on fewer medications. The number of prescribed medications demonstrated significant positive correlations with all assessed renal and hepatic biochemical parameters except eGFR, which showed a significant negative correlation. Because of the cross-sectional design and the between-group differences in disease duration, glycaemic control, and comorbidity burden, these associations should not be interpreted as causal. Nevertheless, they highlight the potential organ-specific risks associated with polypharmacy and underscore the importance of regular biochemical monitoring, structured medication reviews, and individualised therapeutic decision-making in this population.

From a clinical and public health perspective, our findings have several important implications. First, they support the integration of routine renal and hepatic function monitoring into diabetes care protocols, particularly for patients on polypharmacy. Second, they highlight the need for deprescribing initiatives and medication optimisation strategies that prioritise organ safety without compromising therapeutic efficacy. Third, they suggest that the choice of antidiabetic agents should be individualised based on renal and hepatic function, with preferential use of agents with favourable organ safety profiles. Fourth, they underscore the importance of distinguishing between appropriate and inappropriate polypharmacy in clinical decision-making, recognising that the absence of polypharmacy in patients with T2DM may, in some cases, represent under-prescribing and missed opportunities for risk reduction. Future research should employ longitudinal designs with larger sample sizes and multivariable adjustment to confirm these findings, explore the mechanistic pathways linking polypharmacy to organ dysfunction, and evaluate the impact of targeted deprescribing interventions on renal and hepatic outcomes in patients with T2DM.

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