RESEARCH ARTICLE

Association Between Oral Antidiabetic with Unaprpopriate Drug and Microvascular and Macrovascular Complications: An Observational Study

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Abstract

Type 2 Diabetes Mellitus (T2DM) is associated with microvascular complications (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary artery disease, stroke), which contribute significantly to morbidity and mortality. Polypharmacy in the use of Oral Antidiabetic Drugs (OADs) may influence the occurrence of these complications through drug interactions and increased therapeutic complexity. A cross-sectional observational study was conducted involving 100 patients with T2DM. Data were collected from medical records. Variables included the level of OAD polypharmacy and the incidence of complications. Statistical analysis was performed using Spearman rank correlation test. The distribution of complications was 30.8% microvascular, 22.5% macrovascular, and 46.7% other complications. Spearman analysis demonstrated a statistically significant correlation between OAD polypharmacy and the incidence of complications (p=0.017), with a positive correlation of weak-to-moderate strength. OAD polypharmacy is associated with an increased risk of complications in T2DM patients. These findings highlight the importance of rational prescribing and regular therapeutic monitoring to minimize adverse outcomes.

Keywords: Type 2 Diabetes Mellitus, polypharmacy, oral antidiabetic drugs, microvascular complications, macrovascular complications

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Studi Observasional Ketidaksesuaian Penggunaan OAD serta Dampaknya terhadap Komplikasi Mikrovaskuler dan Makrovaskuler

Abstrak

Ketidaksusuaian penggunaan Obat Antidiabetes Oral (OAD) pada pasien Diabetes Mellitus tipe 2 berpotensi memengaruhi kejadian komplikasi mikrovaskuler dan makrovaskuler. Penelitian observasional dengan desain cross-sectional pada 100 pasien Diabetes Mellitus tipe 2. Data diperoleh dari rekam medis. Variabel yang dianalisis meliputi tingkat polifarmasi OAD dan kejadian komplikasi. Analisis menggunakan uji korelasi Spearman Rank. Distribusi komplikasi meliputi mikrovaskuler 30,8%, makrovaskuler 22,5%, dan komplikasi lain 46,7%. Uji Spearman menunjukkan hubungan signifikan antara polifarmasi OAD dan kejadian komplikasi (p=0,017) dengan korelasi positif berkekuatan lemah–sedang. Polifarmasi OAD berhubungan dengan peningkatan risiko komplikasi, kemungkinan akibat interaksi obat dan kompleksitas terapi. Diperlukan evaluasi rasionalitas terapi dan pemantauan berkala.

Kata Kunci: Diabetes Mellitus, polifarmasi, OAD, Mikrovaskuler, Makrovaskuler

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease with a continuously increasing global prevalence and is one of the leading causes of morbidity and mortality. Recent reports indicate that the global burden of diabetes is rising, particularly in developing countries, posing significant challenges to healthcare systems [1]. Chronic hyperglycemia in T2DM contributes to endothelial dysfunction, oxidative stress, and inflammation, which in turn lead to the development of microvascular complications such as retinopathy, neuropathy, and nephropathy, as well as macrovascular complications including coronary artery disease and stroke [2].

Microvascular and macrovascular complications are major determinants of quality of life and prognosis in patients with T2DM. Recent studies have demonstrated that poor glycemic control significantly increases the risk of both microvascular and macrovascular complications, highlighting the importance of effective therapeutic management [3]. In clinical practice, Oral Antidiabetic Drugs (OADs) are widely used as first-line therapy, either as monotherapy or in combination, to achieve optimal glycemic targets.

As the disease progresses and comorbidities such as hypertension and dyslipidemia develop, patients with T2DM are frequently exposed to polypharmacy. Polypharmacy, commonly defined as the use of five or more medications simultaneously, has become a major concern in modern clinical practice due to its association with increased risks of drug interactions, adverse effects, and reduced medication adherence [4]. Furthermore, the complexity of therapeutic regimens may influence clinical outcomes, including glycemic control and the occurrence of complications.

Several recent studies have reported that polypharmacy in patients with T2DM is associated with an increased risk of complications, hospitalization, and higher healthcare costs. On the other hand, combination therapy with OADs is often necessary to achieve therapeutic targets, creating a complex balance between benefits and potential risks [5]. Emerging evidence also suggests that inappropriate medication use in the context of polypharmacy may accelerate the progression of vascular complications. However, the relationship between OAD polypharmacy and the incidence of microvascular and macrovascular complications remains inconsistent across studies. Therefore, an observational study is needed to further evaluate this association. This study aims to analyze the relationship between OAD polypharmacy and the occurrence of microvascular and macrovascular complications in patients with T2DM.

MATERIALS AND METHODS

Study Design and Setting

This study employed an observational analytic design with a cross-sectional approach. The study was conducted at a healthcare facility, utilizing retrospective data collected from patients' medical records over a defined study one year period.

Study Population and Sample

The study population consisted of patients diagnosed with Type 2 Diabetes Mellitus (T2DM) who received Oral Antidiabetic Drugs (OADs). A total of 100 patients were included using a total sampling technique based on predefined inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) patients diagnosed with T2DM, (2) patients receiving OAD therapy, and (3) patients with complete medical record data. Exclusion criteria included patients with incomplete data and those receiving insulin-only therapy without OADs.

Variables and Data Collection

Data were collected from medical records, including patient demographics (age, sex), clinical characteristics (duration of disease, comorbidities), and pharmacological therapy (type and number of OADs).

Polypharmacy was defined as the concurrent use of two or more OADs. The main outcome variable was the occurrence of complications, categorized into: Microvascular complications (retinopathy, neuropathy, nephropathy), Macrovascular complications (coronary artery disease, stroke), and Other complications

RESULTS AND DISCUSSION

The utilization pattern of oral antidiabetic drugs (OADs) in this study indicates a predominance of sulfonylureas and insulin-based regimens, alongside relatively low use of metformin. This trend suggests potential inappropriate prescribing, particularly when considered against contemporary guidelines that recommend metformin

as first-line therapy and early use of agents with proven cardiorenal benefit. The 2022 consensus report in The Lancet Diabetes & Endocrinology emphasizes individualized, evidence-based treatment selection to optimize outcomes and minimize complications [6].

Table 1. Demography Patient Analysis

Category	Amount	Percentage
Microvascular		
Ulcus	30	25%
Kidney failure	4	3.3%
Polyneuropathy	3	2.5%
Total	37	**30.6%**
Macrovascular		
Hypertension	19	15.8%
Dyslipidemia	5	4.2%
Coronary heart disease	3	2.5%
Total	**27**	**22.5%**
Other	56	46.7%
Total	**120**	100%

Inappropriate OAD use—such as delayed treatment intensification, irrational drug combinations, or continued reliance on less optimal agents—has direct implications for microvascular complications. Chronic hyperglycemia remains the primary driver of diabetic retinopathy, nephropathy, and neuropathy. Evidence from major clinical trials demonstrates that inadequate glycemic control significantly accelerates microvascular damage, whereas appropriate pharmacologic management can delay progression. A large-scale review in Diabetes Care highlights that sustained glycemic control is strongly associated with reduced incidence of microvascular outcomes.From a macrovascular perspective, inappropriate selection of OADs may fail to address the high cardiovascular risk inherent in T2DM. Traditional agents such as sulfonylureas, while effective for glucose lowering, do not provide the same cardiovascular protection as newer drug classes. In contrast, sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated significant reductions in major adverse cardiovascular events (MACE). A pivotal trial published in The New England Journal of Medicine confirmed that SGLT2 inhibitors significantly reduce cardiovascular mortality and heart failure hospitalization [7]. Similarly, renal protection and slowing of diabetic kidney disease progression have been well documented [8].

The findings also suggest a broader issue of polypharmacy, which can exacerbate inappropriate prescribing. Polypharmacy increases the risk of drug–drug interactions, adverse drug reactions, and poor adherence, all of which negatively impact glycemic control and vascular outcomes. A recent study in BMC Geriatrics reported that polypharmacy is independently associated with higher rates of complications and hospitalization among T2DM patients [8]. Furthermore, inappropriate OAD use may contribute to glycemic variability and hypoglycemia, particularly with sulfonylureas, which are linked to endothelial dysfunction and increased cardiovascular risk. This reinforces the importance of selecting therapies not only based on glucose-lowering efficacy but also on their safety and long-term vascular benefits.

Another critical issue is the underutilization of cardioprotective antidiabetic agents, which represents a missed opportunity to reduce macrovascular complications. Contemporary evidence strongly supports integrating cardiovascular risk management into diabetes care. A systematic review published in Journal of Clinical Medicine highlights that optimizing antidiabetic regimens with evidence-based agents significantly reduces both microvascular and macrovascular complications.

The present study demonstrates that microvascular complications (30.6%) are more prevalent than macrovascular complications (22.5%), with diabetic ulcers accounting for the largest proportion (25%). These findings reinforce the established understanding that chronic hyperglycemia primarily drives early microvascular damage through mechanisms such as oxidative stress, inflammation, and endothelial dysfunction.

Recent high-impact evidence supports this observation. A comprehensive review by Hauwanga et al. [9] highlights that microvascular complications—including nephropathy, neuropathy, and retinopathy—are strongly linked to sustained hyperglycemia and frequently precede macrovascular disease progression [9]. Furthermore, global epidemiological updates indicate that type 2 diabetes continues to impose a high burden of both microvascular and macrovascular complications, particularly in patients with poor glycemic control and multimorbidity.

From a pharmacotherapeutic perspective, these findings can be closely associated with the use of oral antidiabetic drugs (OADs) and the increasing prevalence of polypharmacy. In clinical practice, patients with type 2 diabetes often require multiple medications to manage hyperglycemia and associated comorbidities, leading to complex treatment regimens. A recent large-scale living systematic review published in *The BMJ* [10] demonstrated that modern glucose-lowering therapies—including SGLT2 inhibitors and GLP-1 receptor agonists—provide significant cardiovascular and renal benefits; however, their effects on microvascular complications remain variable and, in some cases, uncertain [10] . This may partly explain why microvascular complications remain dominant despite pharmacological treatment.

The high prevalence of diabetic ulcers (25%) in this study may indicate suboptimal glycemic control or inadequate therapeutic optimization. Evidence from a recent meta-analysis by Springer Nature (2025) found that non-insulin antidiabetic medications can reduce the risk of microvascular complications; however, their effectiveness depends on appropriate drug selection, adherence, and timely treatment intensification [11]. These findings suggest that simply increasing the number of medications (polypharmacy) does not guarantee improved outcomes unless therapy is rational and individualized.

Polypharmacy itself remains a critical issue in diabetes management. While necessary for controlling multiple risk factors, excessive or inappropriate medication use may increase the risk of drug interactions, reduce adherence, and ultimately contribute to poor clinical outcomes. This is particularly relevant in patients with complications, where treatment regimens become increasingly complex. The coexistence of multiple conditions—such as hypertension, dyslipidemia, and chronic kidney disease—further complicates pharmacokinetics and therapeutic response, potentially diminishing the effectiveness of OADs.

Although macrovascular complications were less prevalent in this study, their long-term clinical significance should not be underestimated. According to the latest International Diabetes Federation (2025), individuals with type 2 diabetes have substantially increased risks of cardiovascular events, including myocardial infarction, stroke, and heart failure, driven by metabolic abnormalities such as hyperglycemia, dyslipidemia, and hypertension [12].The lower prevalence observed in this study may reflect earlier disease stages, underdiagnosis, or partial benefits of pharmacological interventions targeting cardiovascular risk.

Importantly, the proportion of patients without complications (46.7%) suggests a critical window for preventive intervention. Early optimization of OAD therapy, combined with lifestyle modification and regular monitoring, may delay or prevent the onset of complications. However, emerging evidence indicates that diabetes is increasingly associated with multimorbidity and complex disease trajectories, requiring more comprehensive and individualized treatment strategies [3,13].

Overall, the predominance of microvascular complications in this study suggests that current OAD utilization and polypharmacy practices may not yet be fully optimized. While advances in pharmacotherapy have improved cardiovascular outcomes, microvascular complications remain a persistent challenge. Therefore, a rational approach to polypharmacy—emphasizing appropriate drug selection, adherence, periodic medication review, and early treatment intensification—is essential to improve clinical outcomes and reduce complication burden.

Table 2. Inapropriate drug Interaction

Category	Amount	Percentage
Minor		
2-4 drugs	47	47%
Mayor		
5-9 drugs	53	53%
Total	**100**	**100%**

The present study demonstrates that microvascular complications (30.6%) were more prevalent than macrovascular complications (22.5%), with diabetic ulcers representing the most dominant condition (25%). At the same time, a high proportion of patients (53%) were exposed to major polypharmacy (5–9 drugs), indicating a substantial medication burden. These findings highlight the complex relationship between disease progression, complication development, and pharmacological management in patients with type 2 diabetes mellitus (T2DM).

The predominance of microvascular complications is consistent with recent global evidence indicating that chronic hyperglycemia primarily affects small blood vessels, leading to neuropathy, nephropathy, and diabetic foot complications. A 2025 review published in *Biomedicines* emphasized that microvascular damage remains the most common consequence of diabetes and is strongly associated with long-term glycemic exposure and delayed

intervention. This aligns with the high proportion of diabetic ulcers observed in this study, suggesting that glycemic control may not be fully optimized. From a pharmacological standpoint, the high prevalence of polypharmacy (53% major polypharmacy) reflects the increasing complexity of diabetes management. Patients with T2DM often require multiple oral antidiabetic drugs (OADs) in combination with therapies for comorbid conditions such as hypertension and dyslipidemia

However, the coexistence of high polypharmacy and persistent complications suggests that increasing the number of medications does not necessarily lead to better clinical outcomes. A recent systematic review and meta-analysis by Satapathy et al. (2025) reported that polypharmacy is highly prevalent (pooled prevalence ~59%) and is associated with increased risks of medication-related complications, including non-adherence, drug interactions, and hospitalization. This may explain why microvascular complications remain prominent despite extensive pharmacological treatment. In addition, inappropriate or unoptimized OAD use may contribute to ongoing complications. While combination therapy is recommended to achieve glycemic targets, recent evidence suggests that treatment effectiveness depends on rational drug selection, timely intensification, and patient adherence. A real-world study published in *Journal of Diabetes and its Complications* (2025) showed that the addition of newer agents such as GLP-1 receptor agonists can reduce complications and mortality, highlighting the importance of selecting evidence-based therapies rather than simply increasing medication count.

Although macrovascular complications were less prevalent (22.5%), their long-term impact remains significant. Cardiovascular diseases continue to be the leading cause of mortality in T2DM patients, and their development is closely linked to comorbid conditions and metabolic abnormalities. The lower prevalence observed in this study may reflect earlier disease stages, underdiagnosis, or partial benefits of pharmacological interventions targeting cardiovascular risk.

Importantly, the proportion of patients without complications (46.7%) suggests a critical window for early intervention. Optimizing OAD therapy and minimizing inappropriate polypharmacy at this stage may prevent progression to both microvascular and macrovascular complications. However, recent literature emphasizes that diabetes management is increasingly characterized by multimorbidity and therapeutic complexity, requiring a shift toward individualized and patient-centered care.

Overall, the integration of complication and polypharmacy data in this study suggests that while polypharmacy is often necessary in T2DM management, it must be carefully optimized. The persistence of microvascular complications despite high medication use indicates potential gaps in treatment effectiveness, adherence, or clinical monitoring. Therefore, strategies such as rational prescribing, regular medication review, and the use of evidence-based OAD combinations are essential to improve outcomes and reduce complication burden.

Table 3. Drug Used

Drug Category	Amount	Percentage
OAD		
Acarbose	4	0.80%
Aprida flex pen	8	1.70%
Ezelin flex pen	14	2.90%
Gliazide	1	0.20%
Glimepiride	27	5.60%
Gliquidone	6	1.30%
Humalog pen	2	0.40%
Januvia	9	1.90%
Metformin	6	1.30%
Pioglitazone	21	4.40%
Sansulin log pen	12	2.50%
Sansulin rapid pen	4	0.80%
Sitagliptin	1	0.20%
Total	**114**	**24%**
Antibiotic	**93**	**19.4%**
Analgesic	**71**	**14.8%**
Antihypertension	**32**	**6.7%**
Gastoprotector	**33**	**19.4%**
Vitamins	**83**	**25%**
Broncodilator	**5**	**1.00%**
Antihyperurichemia	**4**	**0.80%**

Anchiolithic	3	0.60%
Antiplatelete	14	3.1%
Other	27	17.5%
Total	479	100%

The present study reveals a substantial burden of polypharmacy, with a total of 479 medications prescribed, reflecting the complexity of managing type 2 diabetes mellitus (T2DM) accompanied by multiple comorbidities. OADs constituted 24% of prescriptions, with glimepiride, pioglitazone, and insulin analogs being the most frequently used agents. This pattern suggests a reliance on combination therapy and insulin intensification, typically observed in patients with longer disease duration or inadequate glycemic control.

In comparison with global evidence, the relatively low proportion of metformin (1.3%) contrasts with international recommendations that position metformin as first-line therapy. A large consensus report published in *The Lancet Diabetes & Endocrinology* emphasized metformin as the foundation of pharmacological management due to its cardiovascular safety profile [14]. This discrepancy may indicate late-stage disease presentation or clinical preference for advanced therapies.

The high use of insulin preparations (e.g., flex pens and rapid-acting insulin) supports findings from recent studies indicating that insulin therapy is frequently initiated in patients with poor glycemic control or advanced disease progression. Polypharmacy in such patients is often unavoidable due to the coexistence of cardiometabolic conditions. Indeed, a multicenter study reported that more than half of T2DM patients experience polypharmacy, particularly those with longer disease duration and multiple comorbidities [5].

A notable finding in this study is the high proportion of antibiotics (19.4%) and gastroprotective agents (19.4%), indicating a significant burden of infections and gastrointestinal complications. This aligns with findings from *Diabetes Care*, which reported increased susceptibility to infections among diabetic patients due to immune dysfunction and chronic hyperglycemia. Additionally, the frequent use of gastroprotective agents may reflect the need to mitigate adverse effects of polypharmacy, particularly NSAIDs and antiplatelet drugs.

The largest proportion of medications was vitamins (25%), raising concerns regarding potential overprescribing. Similar trends have been observed in recent pharmacoepidemiological studies, where vitamin supplementation was commonly prescribed despite limited evidence supporting its role in glycemic control or complication prevention. This practice contributes to unnecessary pill burden and may exacerbate issues related to adherence and drug interactions. Furthermore, analgesics (14.8%) and antihypertensives (6.7%) reflect the presence of common comorbidities such as diabetic neuropathy and hypertension. However, the relatively lower use of antihypertensive agents compared to global studies suggests potential under-treatment of cardiovascular risk factors. Given that cardiovascular disease remains the leading cause of mortality in T2DM, this finding highlights an important gap in comprehensive care.

The presence of antiplatelet agents (3.1%) and antihyperuricemia drugs (0.8%) further illustrates the management of macrovascular risk and metabolic complications. However, their limited use may indicate suboptimal implementation of preventive strategies. Evidence suggests that inadequate cardiovascular risk management in diabetic patients contributes significantly to adverse outcomes. Importantly, the observed prescribing pattern reflects the broader issue of polypharmacy-related risks, including drug-drug interactions, adverse drug reactions, and reduced medication adherence. Recent systematic reviews have demonstrated that polypharmacy is strongly associated with increased hospitalization, poor glycemic control, and decreased quality of life in diabetic patients [15].

In addition, studies conducted in Southeast Asia and globally have highlighted that polypharmacy significantly increases the likelihood of drug interactions, particularly involving metformin and cardiovascular medications. This is clinically relevant given the high number of medications observed in this study. Overall, the findings confirm that T2DM patients represent a high-risk population characterized by therapeutic complexity and multimorbidity, where polypharmacy is both necessary and potentially harmful. Recent evidence emphasizes the importance of structured medication review and deprescribing strategies to reduce inappropriate medication use and improve outcomes [16].

CONCLUSIONS

In conclusion, this study demonstrates a significant association between polypharmacy in oral antidiabetic drug (OAD) use and the occurrence of complications in patients with type 2 diabetes mellitus (T2DM). Microvascular complications were more prevalent than macrovascular complications, indicating persistent challenges in glycemic control. The high burden of polypharmacy and evidence of potentially inappropriate prescribing highlight the need

for optimized, guideline-adherent pharmacotherapy. Regular medication review and individualized treatment strategies are essential to reduce complication risk and improve clinical outcomes.

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