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PHARMACOECONOMIC AND CLINICAL ANALYSIS OF ORAL HYPOGLYCEMIC DRUG USE IN TYPE 2 DIABETES MELLITUS IN PRIMARY HEALTH CARE FACILITIES IN AKTOBE, KAZAKHSTAN

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Background. Type 2 diabetes mellitus remains one of the leading causes of chronic morbidity and disability, imposing a substantial clinical and economic burden on healthcare systems. In primary health care settings, effective glycemic control largely depends on the rational prescribing of oral hypoglycemic agents, appropriate dosing, and patient adherence to therapy. However, real-world clinical practice often demonstrates deviations of prescribed daily doses from recommended standards, along with persistent barriers related to drug accessibility and financial constraints. This highlights the need to analyze the structure of oral hypoglycemic drug utilization and the factors influencing the achievement of target glycemic outcomes.

Aim: to analyze the consumption patterns and therapeutic effectiveness of oral hypoglycemic drugs (OHDs) among patients with T2DM in the primary healthcare system of Aktobe, Kazakhstan, while identifying indirect indicators and possible barriers to glycemic control based on prescription patterns and dosage data.

Materials and methods: Data from 386 T2DM patients receiving continuous OHD therapy for at least six months were extracted from the Medical Information System. The analysis focused on drug consumption patterns, defined daily dose (DDD) versus prescribed daily dose (PDD), glycemic outcomes, and comorbidities. HbA1c levels were evaluated to assess treatment effectiveness, while factors influencing therapy adherence and dosing were explored.

Results: Metformin was the most prescribed monotherapy (31.9%), and a combination of sulfonylureas and metformin dominated dual therapy (41.7%). Combination therapy was necessary for 59.1% of patients, indicating the limitations of monotherapy in con-trolling glycemia. Combination therapies involving metformin significantly improved HbA1c levels, especially with sulfonylureas (61%, p = 0.003) and SGLT-2 inhibitors (70.5%, p = 0.039). However, the PDDs of all OHDs were markedly below the WHO DDDs, with metformin's PDD 78% lower. Barriers included medication access and financial constraints.

Conclusions: Optimizing OHD regimens and addressing medication access challenges are essential to improving glycemic control and reducing T2DM complications in resource-constrained environments.

Keywords: *primary health care; type 2 diabetes mellitus; pharmacoepidemiology; drug utilization; oral hypoglycemic drugs; Defined Daily Dose; Prescribed Daily Dose; medication adherence.*

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Резюме

ФАРМАКОЭКОНОМИЧЕСКИЙ И КЛИНИЧЕСКИЙ АНАЛИЗ ПРИМЕНЕНИЯ ПЕРОРАЛЬНЫХ ГИПОГЛИКЕМИЧЕСКИХ ПРЕПАРАТОВ ПРИ САХАРНОМ ДИАБЕТЕ 2 ТИПА В УЧРЕЖДЕНИЯХ ПЕРВИЧНОГО ЗДРАВООХРАНЕНИЯ Г. АКТОБЕ, КАЗАХСТАН

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Актуальность: Сахарный диабет 2 типа остается одной из ведущих причин хронической заболеваемости и инвалидизации, формируя значительную клиническую и экономическую нагрузку на систему здравоохранения. В условиях первичной медико-санитарной помощи эффективность контроля гликемии во многом зависит от рационального назначения пероральных сахароснижающих препаратов, адекватности их дозирования и приверженности пациентов терапии. Однако в реальной клинической практике часто наблюдаются отклонения предписанных суточных доз от рекомендованных стандартов, а также сохраняются барьеры, связанные с доступностью лекарств и финансовыми ограничениями. Это определяет необходимость анализа структуры потребления ПССП и факторов, влияющих на достижение целевых показателей гликемии.

Цель: Изучение структуры потребления и терапевтической эффективности пероральных сахароснижающих препаратов (ПССП) у пациентов с сахарным диабетом 2 типа (СД2) в системе первичной медико-санитарной помощи г. Актобе, Казахстан, а также выявление факторов, препятствующих достижению оптимального контроля гликемии.

Методы: Из медицинской информационной системы были извлечены данные о 386 пациентах с СД2, получавших непрерывную терапию ПССП в течение не менее шести месяцев. Анализ был сосредоточен на структуре потребления лекарств, сравнении определенной суточной дозы (DDD) с предписанной суточной дозой (PDD), гликемических показателях и сопутствующих заболеваниях. Эффективность лечения оценивалась по уровню HbA1c, а также изучались факторы, влияющие на приверженность терапии и дозирование.

Результаты: Метформин был наиболее часто назначаемым препаратом в монотерапии (31,9%), тогда как комбинация метформина с препаратами сульфонилмочевины преобладала в двойной терапии (41,7%). Комбинированная терапия применялась у 59,1% пациентов, что указывает на ограниченную эффективность монотерапии в контроле гликемии. Комбинированная терапия с использованием метформина значительно снижала уровень HbA1c, особенно при сочетании с препаратами сульфонилмочевины (61%, p = 0,003) и ингибиторами SGLT-2 (70,5%, p = 0,039). Однако показатели PDD для всех ПССП были существенно ниже рекомендованных ВОЗ значений DDD, в частности, для метформина — на 78%. Основными барьерами являлись ограниченный доступ к лекарствам и финансовые трудности.

Выводы: Оптимизация дозировок и устранение барьеров доступа к лекарствам необходимы для улучшения гликемического контроля и снижения риска осложнений СД2 в условиях ограниченных ресурсов.

Ключевые слова: *первичная медико-санитарная помощь, сахарный диабет 2 типа, фармакоэпидемиология, использование лекарственных средств, пероральные сахароснижающие препараты, определенная суточная доза, предписанная суточная доза, приверженность терапии.*

Для цитирования:

Кайбагарова И.Б., Аблакимова Н., Смагулова Г.А., Мавлюдова Н., Мусина А.З., Овсянникова А.Н., Сартаева А.Ш., Жамалиева Л.М. Фармакоэкономический и клинический анализ применения пероральных гипогликемических препаратов при сахарном диабете 2 типа в учреждениях первичного здравоохранения г. Актобе, Казахстан // Наука и Здравоохранение. 2026. Vol.28 (1), С. 45-54. *doi 10.34689/SH.2026.28.1.006*

Түйіндеме

ҚАЗАҚСТАН, АҚТӨБЕ Қ., БАСТАПҚЫ ДЕНСАУЛЫҚ САҚТАУ МЕКЕМЕЛЕРІНДЕ 2 ТИПТІ ҚАНТ ДИАБЕТІ КЕЗІНДЕ ПЕРОРАЛДЫ ГИПОГЛИКЕМИЯЛЫҚ ПРЕПАРАТТАРДЫ ҚОЛДАНУДЫҢ ФАРМАКОЭКОНОМИКАЛЫҚ ЖӘНЕ КЛИНИКАЛЫҚ ТАЛДАУЫ

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Өзектілігі. 2-типті қант диабеті созылмалы сырқаттанушылық пен мүгедектіктің жетекші себептерінің бірі болып қала береді және денсаулық сақтау жүйесіне елеулі клиникалық әрі экономикалық жүктеме түсіреді. Бастапқы медициналық-санитарлық көмек жағдайында гликемиялық бақылаудың тиімділігі көбінесе пероральды қант төмендететін препараттарды ұтымды тағайындауға, олардың дозасының жеткіліктілігіне және пациенттердің емге бейілділігіне байланысты. Алайда нақты клиникалық тәжірибеде тағайындалған тәуліктік дозалардың ұсынылған стандарттардан ауытқуы, сондай-ақ дәрілік заттардың қолжетімділігі мен қаржылық шектеулерге байланысты

кедергілер жиі кездеседі. Бұл пероральды қант төмендететін препараттарды тұтыну құрылымын және мақсатты гликемиялық көрсеткіштерге қол жеткізуге әсер ететін факторларды талдаудың қажеттілігін айқындайды.

Мақсаты: Бұл зерттеудің мақсаты – Ақтөбе қаласындағы бастапқы медициналық-санитариялық көмек жүйесінде 2 типті қант диабетімен (2ТҚД) ауыратын науқастарда пероральды қантты төмендететін препараттарды (ПҚТП) тұтыну құрылымын және олардың терапиялық тиімділігін зерттеу және гликемиялық бақылауға қол жеткізуді тежейтін факторларды анықтау болды.

Материалдар мен әдістер: Медициналық ақпараттық жүйеден ПҚТП-ны кемінде алты ай үздіксіз қабылдаған 386 2ТҚД пациенті туралы мәліметтер алынды. Талдау дәрілік тұтыну құрылымына, анықталған тәуліктік доза (DDD) мен тағайындалған тәуліктік дозаның (PDD) салыстырылуына, гликемиялық көрсеткіштер мен қатар жүретін ауруларға бағытталды. Емнің тиімділігі HbA1c деңгейі арқылы бағаланды, сондай-ақ емге бейімділік пен дозалауға әсер ететін факторлар зерттелді.

Нәтижелер: Монотерапияда ең жиі тағайындалған препарат — метформин (31,9%), ал екі компоненттен тұратын емде метформин мен сульфонилмочевина препараттарының комбинациясы жиі қолданылды (41,7%). Құрамдастырылған терапия пациенттердің 59,1%-ына тағайындалды, бұл монотерапияның гликемиялық бақылауда тиімділігінің шектеулі екенін көрсетеді. Метформинге негізделген біріктірілген ем HbA1c деңгейін айтарлықтай төмендетті, әсіресе оны сульфонилмочевина препараттарымен (төмендеу көрсеткіші – 61%, p = 0,003) және SGLT-2 тежегіштерімен (70,5%, p = 0,039) бірге қолданғанда. Алайда барлық ПҚТП бойынша тағайындалған тәуліктік доза (PDD) деңгейі Дүниежүзілік денсаулық сақтау ұйымы (ДДҰ) ұсынған анықталған тәуліктік дозадан (DDD) едәуір төмен болды — мысалы, метформин үшін бұл айырмашылық 78%-ға жетті. Басты кедергілер ретінде дәрі-дәрмектерге қолжетімділіктің шектеулігі мен науқастардың қаржылық мүмкіндігінің төмендігі анықталды.

Қорытынды: Қолданыстағы ресурстар шектеулі жағдайында гликемиялық бақылауды жақсарту және 2-типті қант диабетінің асқыну қаупін азайту үшін дозалауды оңтайландыру мен дәрі-дәрмекке қолжетімділікті арттыру қажет.

Түйінді сөздер: *бастапқы медициналық-санитариялық көмек, 2 типті қант диабеті, фармакоэпидемиология, дәрі-дәрмекті қолдану, пероральды қантты төмендететін препараттар, анықталған тәулік дозасы, тағайындалған тәулік дозасы, емге бейімділік.*

Дәйексөз үшін:

Кайбагарова И.Б., Аблакимова Н., Смагулова Г.А., Мавлюдова Н., Мусина А.З., Овсянникова А.Н., Сартаева А.Ш., Жамалиева Л.М. Қазақстан, Ақтөбе қ., бастапқы денсаулық сақтау мекемелерінде 2 типті қант диабеті кезінде пероралды гипогликемиялық препараттарды қолданудың фармакоэкономикалық және клиникалық талдауы// Ғылым және Денсаулық сақтау. 2026. Vol.28 (1), Б. 45-54. *doi 10.34689/SH.2026.28.1.006*

Background

Type 2 diabetes mellitus (T2DM) has become a global epidemic, affecting millions of people worldwide. According to data from the World Health Organization (WHO), the number of diabetes patients continues to rise, with projections indicating a two-fold increase by 2030 compared to the early 21st century [17]. T2DM is characterized by high prevalence and a significant burden of complications [21]. The treatment of T2DM requires a comprehensive approach, including lifestyle modifications, dietary adjustments, and pharmacological therapy [31]. Oral hypoglycemic drugs (OHD) play a key role in managing this condition by effectively controlling blood glucose levels and reducing the risk of acute and chronic complications such as cardiovascular diseases, nephropathy, retinopathy, and neuropathy [9].

The study of the pharmacoepidemiology of hypoglycemic therapy and drug efficacy is essential for improving the quality of medical care, enhancing clinical outcomes, and optimizing treatment costs. There are two primary areas of pharmacoepidemiological research: evaluating the efficacy and safety of medications and analyzing their consumption. The Anatomical Therapeutic Chemical/ Defined Daily Dose (ATC/DDD) methodology is widely used for standardized assessments of drug consumption levels [2]. This system, developed by the WHO, plays a vital role in studying and comparing drug use at both national and international levels.

Despite the availability of various oral hypoglycemic drugs, there is limited data on their utilization patterns and adherence to treatment guidelines in primary health care settings in the Aktobe region. Understanding these patterns is critical to identifying gaps in the management of T2DM and addressing issues such as suboptimal medication use, patient adherence, and resource allocation.

Given the increasing prevalence of diabetes and its associated complications in the region, this study aims to analyze the consumption of oral hypoglycemic drugs in primary health care facilities in Aktobe. By leveraging the ATC/DDD methodology, the research seeks to evaluate the adequacy of prescribing practices, assess drug utilization trends, and provide evidence-based recommendations for improving diabetes care. The findings are expected to contribute to more efficient management of diabetes, better health outcomes, and optimized use of healthcare resources in the Aktobe region.

For the analysis of the clinical effectiveness of oral hypoglycemic drug therapy, a representative sample of patients was selected to evaluate drug consumption and treatment outcomes in a defined population. The study group was identified from a medical information system database the electronic portal information system of drug provision (ISLO) of the clinic, which included individuals diagnosed with T2DM under outpatient care within the region.

The study included patients aged 18 years and older who were diagnosed with T2DM, exclusively using oral hypoglycemic agents, and under continuous treatment with either a single drug or a combination of drugs for a duration of six months or longer. The key indicator for the effectiveness of diabetes treatment and carbohydrate metabolism compensation was HbA1c levels. This parameter was analyzed twice for 386 patients in their medical records: at the initiation of therapy and during the most recent recorded HbA1c (Glycosylated hemoglobin A1c) measurement under mono- or combination therapy. Additionally, comparisons of body mass index (BMI) and the presence of comorbidities were conducted. Since the analysis was conducted using anonymized data, no ethical approval was required according to prevailing research guidelines.

The study focused on examining the usage trends and clinical effectiveness of oral hypoglycemic drugs (OHDs) in patients with type 2 diabetes mellitus (T2DM) within the primary healthcare system of Aktobe, Kazakhstan, as well as identifying barriers to achieving effective glycemic control.

Methods

A retrospective observational study with pharmacoepidemiological and pharmacoeconomic analysis was conducted at one of the largest polyclinics in Aktobe, Kazakhstan, from September 2024 to January 2025. The study was based on a retrospective analysis of anonymized medical records extracted from the "DamuMed" information system. In accordance with local ethical guidelines, obtaining informed consent from patients was not required since the research involved secondary analysis of anonymized data without direct patient contact. The study was approved by the polyclinic administration under the condition of full data anonymization and subsequent open-access publication. Ethical review was performed by the Ethics Committee of the Marat Ospanov West Kazakhstan Medical University (Protocol No. 11.01.23).

Due to the retrospective nature of the study, direct evaluation of adherence determinants was not feasible; therefore, surrogate measures such as the PDD/DDD ratio and therapy persistence patterns were employed.

Drug Utilization and Effectiveness Analysis.The ATC/DDD methodology was used to assess drug effectiveness and consumption patterns. Recommended by the WHO since 1996, this approach serves as the global standard for drug utilization *research.*

The Defined Daily Dose (DDD) is the conditional average maintenance dose of the drug for its main indication in an adult patient. At the same time, the Prescribed Daily Dose (PDD) reflects the actual amount of the drug prescribed in practice. The comparison of these values (the PDD/DDD ratio) serves as a tool for assessing the compliance of prescribing practices with pharmacotherapy standards, in particular, in the treatment of type 2 diabetes mellitus (DM2). The analysis of discrepancies between DDD and PDD makes it possible to identify potential deviations from optimal dosing, which may be associated with inadequate glycemic control. Significant differences between the prescribed and standard dose (for example, a significant excess or underestimation of the PDD/DDD value) may indicate the risk of ineffective therapy, overdose, or a subtherapeutic effect.

Formula for PDD calculation:

PDD = (Dose per tablet × Number of tablets per pack × Number of issued packs)/ (Number of patients receiving the drug for one year × 365 days)

Pharmacological Grouping and Prescription Frequency

The sample data for pharmacoeconomic analysis were processed by categorizing drugs based on treatment regimens and pharmacological groups. The frequency of each specific drug prescription was calculated as a proportion of the total prescriptions in the group (Table 1).

Table 1.

Baseline Characteristics of the Study Population.

Demographic characteristic	Value
Age, years	63 ±8,9
Female, n	213 (55,2%)
HbA1c	8,34 ±2,48
BMI, kg/m2	31,51 ±5,1
Comorbidities, n	
Arterial hypertension	340 (88,1%)
Coronary heart disease	17 (4,4%)
Retinopathy	35 (9,1%)
Angiopathy	6 (1,6%)
Polyneuropathy	6 (1,6%)

All data are expressed as n (%), mean ±SD. HbA1c - Glycosylated hemoglobin A1c, BMI – Body Mass Index.

Cost Analysis

The average cost per mg (in KZT) was calculated for each oral hypoglycemic agent as follows:

Average cost per mg (KZT) = Cost of 1 pack/(Number of tablets in a pack × mg per tablet)

The average annual treatment cost per patient was calculated as:

Annual cost per patient (KZT /year) = Weighted average cost per mg × PDD (mg/day) × 365 days

Statistical Analysis

The comparison of glycated hemoglobin (HbA1c) levels at the initiation of treatment and at the time of the last recorded measurement for all hypoglycemic therapy regimens, as well as changes in body mass index (BMI), was conducted using the Wilcoxon signed-rank test. The study design was longitudinal, which allowed for the assessment of changes in these parameters over time. The obtained p-value was 0.003, with a significance level set at $p < 0.05$.

Results

Characteristics of the Study Population

The study included a total of 386 patients with T2DM who met the inclusion criteria. These patients were selected from a larger cohort of 1,536 individuals registered in the "DamuMed" Medical Information System database, representing adult patients under outpatient care in a city polyclinic with a population coverage of 51,738 people. All participants were aged 18 years and older and were receiving oral hypoglycemic therapy for a continuous duration of at least six months. Statistical analyses were performed using SPSS version 25 (IBM Corp., 2019). Key

demographic and clinical characteristics of the study population are summarized in Table 1.

The studied patients with T2DM received various oral hypoglycemic agents, including both monotherapy and combination regimens. The monotherapy options included DPP-4 inhibitors, SU derivatives, and SGLT-2 inhibitors.

The combination therapy included:

1. Dual combinations, such as sulfonylurea derivatives with DPP-4 inhibitors or SGLT-2 inhibitors, as well as combinations of metformin with SGLT-2 inhibitors, DPP-4 inhibitors, or repaglinide.

2. Triple combinations involving sulfonylurea derivatives, metformin, and SGLT-2 inhibitors.

A frequency analysis of oral glucose-lowering therapy in patients with T2DM revealed that 41.9% of patients received monotherapy, while 59.1% were on combination therapy. Among the monotherapy regimens, metformin was the most frequently prescribed (31.9%). Among various hypoglycemic therapeutic regimens, the combination of sulfonylurea derivatives and metformin was the most common (41.7%).

Other groups of oral hypoglycemic drugs accounted for only a small fraction of the overall drug consumption structure: monotherapy with sulfonylureas was received by 2.8% of patients, DPP-4 inhibitors by 5.2%, and only four patients were pre-scribed a drug from the SGLT-2 inhibitor group. The combination of metformin with SGLT-2 inhibitors accounted for 3.1%, with DPP-4 inhibitors 7.8%, and with repaglinide 0.8%. The combination of sulfonylureas with SGLT-2 inhibitors accounted for 0.5% and with DPP-4 inhibitors for 0.8%. A triple combination of MET, SUs, and SGLT-2 inhibitors accounted for 4.4%. (Table 2).

As a result of analyzing and comparing data before and after the therapy, the proportion of patients in the overall group with HbA1c levels >8% decreased from 47.4% to 37.6%, while the proportion of patients with HbA1c levels <7% increased from 23.6% to 30.6%. These changes indicate positive dynamics in glycemic control as a result of the therapy (Figure 1). These results emphasize underdosing trends that may reflect both physician caution and systemic limitations in drug accessibility.

Comparison of Glycated Hemoglobin (HbA1c) Levels Before and After Treatment

A comparison of HbA1c levels at the start of treatment and at the time of the last registration among all hypoglycemic therapeutic regimens revealed a statistically significant reduction in only two groups of T2DM patients:

1. Based on the analysis using the Wilcoxon signed-rank test, statistically significant differences were identified in HbA1c levels in the overall group before and after treatment. The Z value was -3.844, and the asymptotic two-tailed significance ($p < 0.001$) indicates a high statistical significance of the differences ($p < 0.05$) in 32.4% of patients.

2. In the group receiving combination therapy with metformin and sulfonyl-urea derivatives, a reduction was observed in 61% of patients (Wilcoxon signed-rank test, $p = 0.003$ at a significance level of $p < 0.05$).

3. In the group treated with a combination of sulfonylureas, sodium-glucose co-transporter 2 inhibitors (SGLT-2), and metformin, a reduction was observed in 70.5% of patients ($p = 0.039$).

These results suggest that patients receiving this combined hypoglycemic therapy achieved better glycemic control. However, most T2DM treatment regimens did not demonstrate statistically significant reductions in HbA1c levels. This indicates insufficient treatment efficacy or limited access to necessary medications for patients.

Table 2.

Treatment Schemes for Patients with Type 2 Diabetes.

Treatment Regimen	Number of Patients (n=386)	%
Monotherapy		
- Biguanides (Metformin)	123	31.9
- Sulfonylurea derivatives:	11	2.8
- Gliclazide	9	2.3
- Glimepiride	2	0.5
- DPP-4 inhibitors:	20	5.2
- Vildagliptin	11	2.86
- Linagliptin	9	2.34
- SGLT-2 inhibitors:	4	1.0
- Dapagliflozin	1	0.25
- Canagliflozin	3	0.75
Combination Therapy		
- Sulfonylurea + Metformin:	161	41.7
- Gliclazide + Metformin	145	37.56
- Glimepiride + Metformin	16	4.13
- Sulfonylurea + SGLT-2:	2	0.5
- Gliclazide + Dapagliflozin	2	0.5
- Sulfonylurea + DPP-4:	3	0.8
- Gliclazide + Linagliptin	2	0.53
- Gliclazide + Vildagliptin	1	0.26
- Metformin + SGLT-2:	12	3.1
- Metformin + Dapagliflozin	3	0.77
- Metformin + Empagliflozin	5	1.55
- Metformin + Canagliflozin	3	0.77
- Metformin + Repaglinide	3	0.8
- Metformin + DPP-4:	30	7.8
- Metformin + Vildagliptin	18	4.68
- Metformin + Linagliptin	12	3.12
- Metformin + Sulfonylurea + SGLT-2:	17	4.4
- Metformin + Gliclazide + Empa	6	1.55
- Metformin + Gliclazide + Dapa	2	0.88
- Metformin + Gliclazide + Cana	6	1.55
- Metformin + Glimepiride + Empa	1	0.44
- Metformin + Glimepiride + Cana	1	0.44

DPP-4 - dipeptidyl peptidase-IV inhibitors;
SUs – Sulfonylureas;
SGLT-2 - sodium–glucose cotransporter 2 inhibitors.

Assessment of Drug Accessibility Using the ATC/DDD Methodology

To evaluate the accessibility of hypoglycemic drugs, the ATC/DDD methodology was applied. This allowed for calculating the average prescribed daily dose (PDD) and comparing it to the defined daily dose (DDD) recommended for each drug. The ratio of PDD to DDD provides insights into the adequacy of treatment with drugs used for T2DM management.

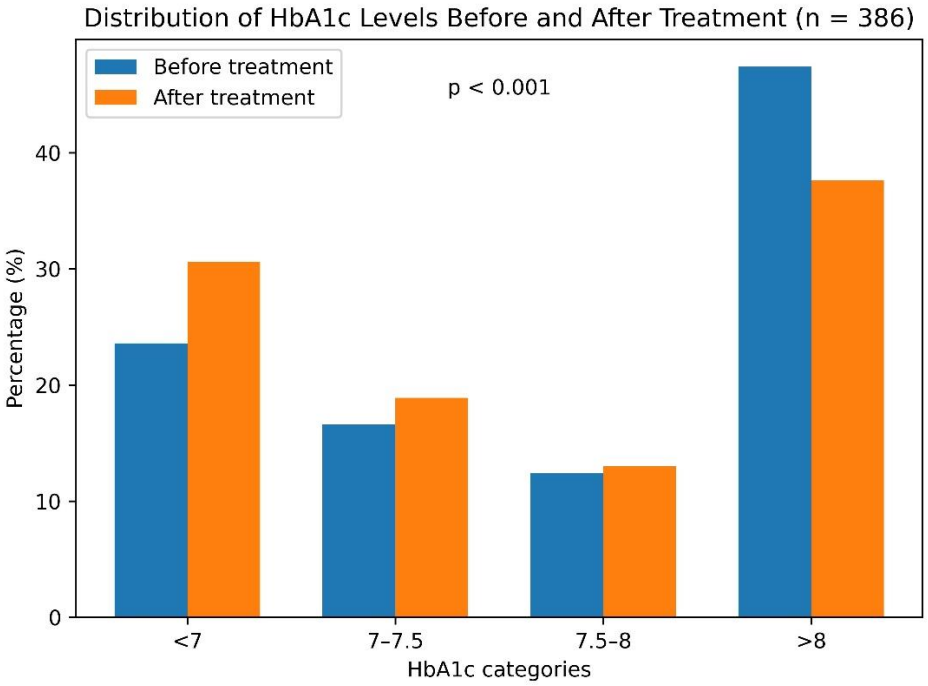

Figure 1. Comparison of HbA1c results.

Analysis of oral hypoglycemic drug use revealed a clear difference between the defined daily doses (DDD) recommended by the World Health Organization and the actual prescribed daily doses (PDD) used in clinical practice (Table 3). Across all pharmacological classes, the prescribed doses were consistently below the international standards. Metformin and sulfonylureas were the most frequently used, yet both were prescribed at substantially lower doses than the WHO DDD values. Similar trends were observed for DPP-4 and SGLT-2 inhibitors, where the PDD/DDD ratios ranged from 0.17 to 0.24, reflecting limited access to newer and more expensive drugs. These findings highlight the underdosing tendency typical of resource-constrained settings and indirectly point to barriers such as medication cost and patient adherence. (Table 3).

Table 3.

Therapeutic profile of consumption of oral hypoglycemic drugs by ATC classification groups in monetary and quantitative terms, indicating the prescribed and established daily doses.

Drug class	International Nonproprietary Names	WHO DDD (unit*)	Mean PDD (unit*)	PDD/DDD ratio	Mean annual cost per patient (KZT)
Biguanides	Metformin	2	0.43	0.20	2 982
Sulfonylureas	Gliclazide / Glimepiride	60	35.8	0.59	3 920
DPP-4 inhibitors	Vildagliptin / Linagliptin	0.1 / 5	0.014 / 1.2	0.24	27 635
SGLT-2 inhibitors	Dapagliflozin / Empagliflozin / Canagliflozin	10 / 10 / 0.2	1.7 / 2.0 / 0.04	0.17 – 0.20	34 122

**PDD (Prescribed Daily Dose) – The average prescribed daily dose of a medication, characterizing the average level of drug consumption per day by a patient in real clinical practice. DDD – The average defined daily dose of a medication, used for its main indication in adults.*

** Unit corresponds to WHO ATC/DDD Index definition for each drug (mg or g depending on the molecule).*

Microvascular and Macrovascular Complications

The prevalence of microvascular complications in T2DM patients was as follows:

- Peripheral polyneuropathy: 1.6%
- Diabetic retinopathy: 9.1%
- Diabetic nephropathy: 4.4%

Additionally, 38.6% of T2DM patients had coronary artery disease, and 88.1% had arterial hypertension. These comorbidities require concurrent treatment with T2DM, complicating therapy adherence and glycemic control. Studies confirm that the presence of comorbid conditions and the necessity of their treatment can decrease adherence to primary therapy due to increased medication burden, complex regimens, and potential side effects [13].

Body Mass Index (BMI) and Therapy Effectiveness

The Wilcoxon test demonstrated that, in most cases, changes in BMI did not reach statistical significance (asymptotic significance > 0.05) with various drug combinations. This suggests a lack of pronounced effect in some therapy regimens.

Recent studies highlight a strong correlation between BMI and treatment adherence, especially in interventions involving diet and physical activity. Poor adherence to lifestyle recommendations is directly linked to limited BMI changes. While short-term success is achievable, maintaining long-term adherence remains challenging due to factors such as lifestyle pressures and limited post-intervention support.

Discussion

The choice of diabetes treatment regimens depends not only on the individual characteristics of patients but also on many other factors, including the experience of doctors, the availability of medications, and the peculiarities of healthcare systems in different countries [25]. The study analyzed medical records of 386 patients with type 2 diabetes in Aktobe, Kazakhstan, focusing on the use of oral hypoglycemic drugs (OHDs) in primary care. Treatment patterns were identified and compared with findings from studies by *Gazzaz Z.J. et al. and Yousefi N. et al.* [16, 37].

The pharmacoepidemiology of T2D treatment in primary healthcare in 2023 included nine subgroups of OHDs based on the ATC classification, used either as monotherapy or in various combinations. According to the American Diabetes Association® (ADA) and the European Association for the Study of Diabetes (ADA/EASD 2022) recommendations, MET is recommended as a first-line drug for T2D treatment due to its proven efficacy, safety, and affordability [12]. This advantage was most prominently demonstrated in studies such as the UKPDS (United Kingdom Prospective Diabetes Study) [22], which showed reductions in HbA1c levels and cardiovascular risk with long-term use, particularly in the early stages of the disease.

Despite over 60 years of clinical application, various factors related to physicians and patients may contribute to insufficient adherence and negatively impact treatment effectiveness [32]. The results of a meta-analysis of randomized controlled trials confirmed that combination therapy including MET significantly reduces HbA1c levels [32,9]. These findings are consistent with recommendations to transition to combination therapy when glycemic control is insufficient with monotherapy. According to a 1999 study by Turner et al., more than 30% of patients require intensification of therapy within the first two years after starting MET treatment and more than 50% within three years [35].

The principles of rational prescribing were generally adhered to in accordance with the WHO-recommended criteria for medication use. The most frequently prescribed drugs were metformin and its combination with sulfonylureas (SUs), accounting for 31.9% and 41.7% of patients (Fig. 1), respectively [32]. The high popularity of these drug groups can be attributed to their accessibility, low cost, and cost-effectiveness. The combination of metformin and SUs has a synergistic effect [29,23], leading to a significant reduction in HbA1c levels compared to monotherapy, as de-scribed in the study by Abu Reid I.O. et al. [2]. The low doses of metformin and SGLT-2 inhibitors observed in this study align with findings from other research conducted in resource-limited countries such as India and Brazil. Studies by Das A.K. et al. show that financial and social factors significantly affect drug availability and patient adherence to treatment [11]

Moreover, the high frequency of combination therapy identified in this analysis underscores the need for more intensive glycemic control in patients. More than half of the patients (59.1%) required combination therapy, reflecting the inadequacy of monotherapy in achieving sufficient glycemic control. A similar trend was observed in studies conducted in Eastern Europe and Central Asia, where combination therapy is also widely used to achieve target glycemic levels [26,34].

The reduction in HbA1c levels by 0.6–0.9% through combination therapy demonstrates its high efficacy in achieving glycemic control in T2D patients. The use of drugs from different classes allows for addressing various pathophysiological mechanisms of hyperglycemia [10,36], offering flexibility and enhanced treatment out-comes. However, international studies indicate that combination therapy may be associated with an increased risk of hypoglycemia and weight gain, requiring careful patient monitoring [24,5,28,15].

According to the American Diabetes Association (ADA) guidelines, the target HbA1c level should be maintained below 7% [26]. In this study, a comparative analysis of HbA1c levels before and after treatment showed that the target level was achieved in only 32.4% of patients, highlighting the need for further improvements in therapeutic approaches. The Z-value was -3.844, and the asymptotic two-tailed significance ($p < 0.001$) indicated a high statistical significance of the results. However, most treatment regimens did not achieve sufficient HbA1c reduction in a significant proportion of patients, necessitating a detailed analysis of drug utilization using the ATC/DDD methodology to account for prescription specifics. The consistent underdosing (PDD < DDD across all classes) may serve as an indirect indicator of both therapeutic caution and financial barriers, indirectly reflecting adherence challenges.

Further calculations of the prescribed daily dose (PDD) to the defined daily dose (DDD) recommended by WHO experts revealed significant discrepancies for all medications (Table 3). These differences may be attributed to physiological characteristics, pharmacokinetics, pharmacodynamics, and cultural or medical practices in different countries, as noted by the WHO Collaborating Center for Drug Statistics Methodology. The prescribed daily doses (PDD) in patients of Asian descent are usually lower than those of Caucasians, which may be due to lower body weight, slower metabolism, limited access to medications, and a more cautious approach to prescribing therapy [27,14]. In addition, WHO indicates that the average PDD for oral hypoglycemic agents is often lower than the established DDD. This is due to the use of combined treatment regimens with reduced doses to reduce the risk of side effects, as well as individualization of therapy based on age, body weight, kidney function, and glycemic levels [28].

Alongside the ATC/DDD analysis, a financial review based on data from 3,807 patients was conducted. The total annual cost of all types of therapy amounted to 29,039,701 KZT (approximately USD 64,532.6). The average annual treatment cost per patient was 7,627.97 KZT (~USD 16.95). Such drugs had a higher cost compared to others, such as metformin (2,982.05 KZT /patient annually). Metformin remained the most economically advantageous option due to its low per-patient treatment cost and high usage rate. New-generation drugs, such as SGLT-2 inhibitors (empagliflozin at 146,029.2 KZT /patient annually) and DPP-4 inhibitors (linagliptin at 27,635.3 KZT /patient annually), were more expensive, as noted in Bang C. et al.'s study [7] which limited their widespread use. The average annual treatment cost per patient was USD 4.2 (1,976 KZT)

for metformin, USD 0.67 (314 KZT) for glimepiride, and USD 1.74 for gliclazide. In comparison, M. Bekele et al. reported that in Chile in 2019, the annual cost per patient was USD 70 for metformin and USD 217 for sulfonylureas (SU) [8,6].

New drug classes such as SGLT-2 and DPP-4 inhibitors were rarely prescribed and at lower doses, which limited their potential for improving glycemic control and reducing complications. The reasons may include high costs that restrict their availability to low-income patients; in clinical practice, there is often an emphasis on more affordable and time-tested drugs like metformin and SUs.

The effectiveness analysis of various therapeutic regimens revealed significant HbA1c reductions only in two patient groups. Among patients receiving combination therapy with metformin and SUs, the proportion achieving target levels was 61% ($p = 0.003$). In the group using a combination of SUs, SGLT-2 inhibitors, and metformin, the proportion reached 70.5% ($p = 0.039$).

Despite the statistically significant HbA1c reductions in specific groups with combination therapy, the overall efficacy of most treatment regimens remained insufficient. The proportion of patients with HbA1c >8% decreased from 47.4% to 37.6%. While this is a positive result, it underscores the suboptimal nature of current treatment approaches. Achieving lower HbA1c values requires further improvement in therapeutic strategies. These results may be due to limited availability of modern drugs, the use of low dosages, or insufficient treatment intensification in cases of inadequate disease control. Factors such as therapy efficacy, adherence to treatment regimens, irregular medication intake, or restricted access to modern and effective drugs may also contribute [20,3,30].

The average age of the patients studied was 63±8.9 years. Analysis revealed the following microvascular complications of T2DM: lower extremity polyneuropathy – 1.6%, diabetic retinopathy – 9.1%, and diabetic nephropathy – 4.4%. Macrovascular complications such as ischemic heart disease were observed in 38.6% of T2DM patients, and arterial hypertension in 88.1%. Thus, patients had comorbidities requiring treatment alongside T2DM. Similar studies confirm that the presence of comorbidities and the need for their treatment can reduce adherence to primary therapy [5]. This is associated with an increased number of medications, complex treatment regimens, and potential side effects, often leading to reduced discipline in taking medications [1]. Studies by Al Shidhani A. et al. indicate that polypharmacy is significantly associated with patient age, the presence of comorbidities, and the duration of T2DM. For example, elderly diabetes patients often suffer from arterial hypertension, dyslipidemia, and other chronic conditions requiring additional medications and increasing the risk of drug interactions [4,33].

Although adherence data were not directly measured, the low PDD/DDD ratios and the predominant use of affordable drugs (e.g., metformin and sulfonylureas) suggest that financial and accessibility barriers substantially influence treatment adherence in this population. These findings align with prior studies in low-resource settings [11,20,32].

Despite its strengths, the study has several limitations. First, the retrospective design was based on medical documentation and drug supply systems, which may not fully reflect patient adherence, clinical outcomes, or off-label drug use. Second, the study was conducted in a single city, which may limit its generalizability to other regions of Kazakhstan or countries with different healthcare systems. Third, the analysis did not cover long-term outcomes or complications beyond the study period. Finally, factors such as socioeconomic status, patient education levels, and medical practitioner practices, which may influence drug prescriptions and treatment adherence, were not thoroughly analyzed. The single-center nature of the study limits generalizability. Future multi-center studies across different socioeconomic regions of Kazakhstan are needed to validate these findings.

Conclusion

This study provides a comprehensive analysis of oral hypoglycemic drug (OHD) consumption in primary healthcare settings in Aktobe, Kazakhstan, offering valuable insights into current treatment practices and their limitations. The frequent use of metformin both as monotherapy and in combination regimens emphasizes its fundamental role in the pharmacological management of T2DM.

However, significant discrepancies between prescribed daily doses and WHO-recommended defined daily doses highlight barriers such as drug accessibility, financial constraints, and adherence challenges.

Combination therapies involving metformin with sulfonylureas or SGLT-2 inhibitors were effective in improving glycemic control, with statistically significant reductions in HbA1c levels. Yet, the overall proportion of patients achieving optimal glycemic targets remains suboptimal, emphasizing the need for tailored interventions to enhance therapy adherence and access to newer drug classes.

Addressing these challenges requires a multipronged approach, including policy measures to improve drug affordability, educational initiatives to strengthen patient adherence, and broader access to advanced therapies. These actions can substantially optimize diabetes management, reduce complication risks, and improve patient outcomes in resource-limited settings such as Aktobe. Future research should focus on longitudinal analyses involving larger and more diverse populations to validate and extend these findings. Expanding the dataset beyond a single city will provide a more comprehensive understanding of prescribing trends across Kazakhstan. Therefore, these results emphasize the importance of developing national health policies to ensure equitable access to modern oral hypoglycemic drugs, particularly for patients managed in primary health care settings.

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