BMJ Open

Oral antidiabetic medication adherence and glycaemic control among patients with type 2 diabetes mellitus: a cross-sectional retrospective study in a tertiary hospital in Saudi Arabia

Bander Balkhi,[1] Monira Alwhaibi,[1] Nasser Alqahtani,[2] Tariq Alhawassi,[1,3] Thamir M Alshammari,[3,4] Mansour Mahmoud,[5] Mansour Almetwazi,[1] Sondus Ata,[6] Khalid M Kamal[7]

To cite: Balkhi B, Alwhaibi M, Alqahtani N, *et al*. Oral antidiabetic medication adherence and glycaemic control among patients with type 2 diabetes mellitus: a cross-sectional retrospective study in a tertiary hospital in Saudi Arabia. *BMJ Open* 2019;**9**:e029280. doi:10.1136/bmjopen-2019-029280

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-029280).

Received 25 January 2019
Revised 20 June 2019
Accepted 3 July 2019

For numbered affiliations see end of article.

Correspondence to
Dr Bander Balkhi;
bbalkhi@ksu.edu.sa

ABSTRACT

Objectives The purpose of this study is to measure the adherence rates of oral antidiabetic drugs (OADs) in patients with type 2 diabetes mellitus (T2DM) and assess the relationship of glycaemic control and adherence to OADs after controlling for other associated factors.

Design Cross-sectional retrospective study.

Setting Large tertiary hospital in the central region of Saudi Arabia.

Participants 5457patients aged 18 years and older diagnosed with T2DM during the period from 1 January 2016 to 31 December 2016.

Primary and secondary outcome measures The modified medication possession ratio (mMPR) was calculated as a proxy measure for adherence of OADs. The factors associated with OADs non-adherence and medication oversupply were assessed using multinomial logistic regression models. The secondary outcomes were to measure the association between OADs adherence and glycaemic control.

Results Majority of patients with T2DM were females (n=3400, 62.3%). The average glycated haemoglobin was 8.2±1.67. Among the study population, 48.6% had good adherence (mMPR >0.8) and 8.6% had a medication oversupply (mMPR >1.2). Good adherence was highest among those using repaglinide (71.0%) followed by pioglitazone (65.0%) and sitagliptin (59.0%). In the multivariate analysis, women with T2DM were more likely to have poor adherence (adjusted OR (AOR)=0.76, 95% CI=0.67, 0.86) compared with men. Also, medication oversupply was more likely among patients with hyperpolypharmacy (AOR=1.88, 95% CI=1.36, 2.63), comorbid osteoarthritis (AOR=1.72, 95% CI=1.20, 02.45) and non-Saudi patients (AOR=1.53, 95% CI=1.16, 2.01). However, no association was found between glycaemic control and adherence to OADs.

Conclusion The study findings support the growing concern of non-adherence to OADs among patients with T2DM in Saudi Arabia. Decision makers have to invest in behavioural interventions that will boost medication adherence rates. This is particularly important in patients with polypharmacy and high burden of comorbid conditions.

Strengths and limitations of this study

- ► This study provides a real insight into the current status of medication adherence rates among patient with type 2 diabetes mellitus (T2DM) in Saudi Arabia.
- ► Using real-world data of more than 5000 patients with T2DM in Saudi Arabia, the study assesses the impact of adherence among different patient subgroups.
- ► This study did not control the severity of diabetes or diabetes complications, which may affect the rate of adherence to oral antidiabetic drugs (OADs).
- ► This study indirectly measured adherence to OADs using patient electronic health records, which may not reflect the actual adherence rate.
- ► Findings from this study cannot be generalised to different populations and settings.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a highly prevalent chronic progressive disorder characterised by high glucose levels in the blood.[1] The estimated global prevalence in the adult population was 8.8% in 2015[2] and is projected to increase to 10.4% by 2040.[2] In Saudi Arabia, the estimated prevalence of T2DM is approximately 23%[3 4] with another 25.5% of the population (30 years and older) classified as pre-diabetes. By 2035, the prevalence of T2DM in Saudi Arabia is projected to double and is expected to reach an estimated 7.5 million cases.[5] While diabetes is projected to be the seventh leading cause of mortality and disability worldwide by 2030,[6] it is already the sixth leading cause of death

in Saudi Arabia based on the WHO report.[7] It is well established that uncontrolled T2DM is associated with negative health consequences such as blindness, kidney failure, lower limb amputation and other complications, all of which result in poor quality of life in patients.[8 9] Also, T2DM is a well-established risk factor for cardiovascular disease (CVD) and macrovascular complications including costly conditions like coronary heart disease, stroke, nephropathy, retinopathy and others.[10 11] A meta-analysis concluded that the risk of CVD in patients with diabetes was three times compared with those without diabetes.[11]

Worldwide, diabetes imposes a large economic burden on the individuals and national healthcare systems. A recent study estimated the global cost of diabetes in adult patients at US$1.31 trillion, which represents 1.8% of the global gross domestic product.[12] Two-third of this cost was direct medical cost while the remaining one-third was attributable to indirect cost such as loss in productivity.[12] In the Middle East and North Africa regions, the rising prevalence of diabetes is projected to increase the healthcare cost by 67% by 2045.[3] Similar trends are being observed in Saudi Arabia as well and the medical healthcare expenditure for people with diabetes is 10 times higher (US$3686 vs US$380) than those without the condition.[13] Diabetes and its complications also result in high indirect costs such as costs related to absenteeism, loss of productivity, disability and premature mortality. The overall economic burden of diabetes in Saudi Arabia is substantial with an estimated direct cost of 17 billion Saudi Riyals (US$4.5 billion) in 2014, which is expected to increase to 43 billion Saudi Riyals (US$11.4 billion) in the future.[14]

Patient adherence to recommended treatment regimen is one of the key contributors to quality health outcomes in T2DM. The benefits of drug therapy in terms of improved glycaemic control and subsequent reduction in microvascular, macrovascular complications and morbidity have been fairly demonstrated. Adherence to oral antidiabetic drugs (OADs) is associated with better glycaemic control,[15 16] reduced risk of diabetes complications and reduced economic burden.[17 18] Investigators in Spain reported that a change in glycated haemoglobin (HbA1c) between the first and last patient visits was largely driven by OADs adherence in 13% of the cases.[19] In Saudi Arabia, nearly 56% of patients have been shown to have low medication adherence.[20]

Although poor adherence (medication underuse) is a well-recognised issue in any healthcare setting, having excess supply of medications than needed (medication oversupply) may also lead to negative health outcomes such as increase in toxicity risks, inefficient use of available healthcare resources and increase in unnecessary healthcare costs.[21] Prevalence of oversupply has been shown to vary across different institutions, medication classes and countries and ranges from 11% to 53%.[22] Medication oversupply was common, especially among T2DM patients, which may increase the risk of hospitalisation[23–26] and further influence achieving the recommended level of HbA1c.[27]

With the prevalence of T2DM increasing at an alarming rate in Saudi Arabia, there is an urgent need to address non-adherence to positive interventions, such as OADs, so as to reign in the rapid escalation of healthcare costs and improve patient outcomes. Although several studies have measured the adherence and oversupply rate in patients with diabetes, their prevalence among patients with T2DM in Saudi Arabia along with their impact on glycaemic control is largely unknown.[28–31] The purpose of this study was to evaluate adherence to OADs and to explore the variables associated with OADs non-adherence in patients with type 2 diabetes. The association between glycaemic control and adherence to OADs will also be examined.

METHODS

Study design and setting

A retrospective study was conducted in King Saud University Medical City (KSUMC), the largest tertiary teaching hospital located in the central region of Saudi Arabia. KSUMC is equipped with more than 1200 beds and provides a wide array of medical services. The patient population is composed mainly of Saudi citizens who are predominantly residents of the capital city Riyadh but the hospital also serves as a referral centre for the whole country. The study was approved by the institutional review board (IRB) at KSUMC (IRB number: E-16-2203).

Data sources

Patients with a recorded diagnosis of T2DM (using International Classifications of Diseases—ninth edition, Clinical Modification codes) and receiving OADs at outpatient clinics of KSUMC were retrospectively identified from the electronic health records (EHRs) for the period 1 January–30 December 2016. The extracted data included demographic information (age, gender, marital status, nationality), laboratory data (HbA1c) and prescription data (name of prescription filled; dispensing date; quantity of drug; number of days supplied and refills). All the data were extracted from the EHRs and there was no direct involvement of any patient in the study. Patient consent was therefore not required and all study variables were collected retrospectively and anonymously (de-identified data) from EHRs.

Study population

Patients aged 18 years and older with T2DM who had received their treatment at outpatient clinics at KSUMC during the study period had at least two prescription fills for one of the following OADs: sulfonylureas (glibenclamide); biguanides (metformin), thiazolidinediones (pioglitazone), meglitinide analogues (repaglinide), glucosidase inhibitor (acarbose), oral dipeptidyl peptidase-4 inhibitor (sitagliptin) and combination therapy were included in the study. Patients on insulin or incretin

mimetics (liraglutide injection) and those without at least one HbA1C value were excluded from this study.

Patient and public involvement

Patients and public were not involved in the design or conduct of this study.

OUTCOME MEASURES

Primary outcome: adherence to OADs

The modified medication possession ratio (mMPR) was used as a proxy to measure the adherence rate in this study. The mMPR was chosen as it is one of the most commonly reported adherence assessment method using EHRs and administrative claims data in the literature.[24 32–35] Also, as one of the aims of this study is to estimate the oversupply rate, mMPR allows for calculation of medication oversupply over 100% while in other assessment methods such as the proportion of days covered, any medication oversupply (over 100%) is truncated.[36] The mMPR was calculated as the sum of the total days supply for all OADs fills divided by the sum of the number of days covered and the last refill days.[18 19] The date of the first prescription fill was designated as the index date. The total days supplied for each OAD was calculated from the index date until the end of 2016. Patients were considered adherent to their medication regimen if the estimated mMPR ≥0.8. Otherwise, the patients were deemed as poorly adherent. An mMPR value greater than 1 indicated that the patients filled their medications early before entirely consuming their preceding stock of medications; thus, they had excessive medications than needed. Medication oversupply was defined as mMPR ≥1.2; the cut-off point of 20% difference in supply has been reported as an acceptable range in several studies.[23 25] In this study, adherence was categorised into: poor adherence (mMPR <0.8), good adherence (mMPR ≥0.8 to <1.2) and oversupply (mMPR ≥1.2).[37] The mMPR was calculated separately for each OAD prescribed during the 12-month study period. Then, an average mMPR was calculated with equal weighting of each drug class.

Secondary outcome: association between OADs adherence and glycaemic control

The secondary outcome of glycaemic control was based on the patient's last HbA1c reading. The American Diabetes Association Standards of Care has recommended that HbA1c<7% should be the glycaemic goal for adults with T2DM.[38] Using this threshold, the HbA1c was classified into two categories: <7% indicating good glycaemic control and ≥7% indicating poor glycaemic control. The last HbA1c reading was used to determine the relationship between adherence and glycaemic control.

Independent variables

Independent variables included age groups, gender, marital status, nationality and diagnosed comorbid chronic conditions (hypertension, heart failure, ischaemic heart disease, dyslipidaemia, cancer, chronic kidney disease, asthma, osteoarthritis, osteoporosis, depression and anxiety).[39 40] In addition, polypharmacy was calculated for each patient in this study. Although there is no consensus on the threshold regarding the number of medications used by patients to be considered as polypharmacy, the most accepted definition of polypharmacy is the use of five or more drugs.[41] Based on this threshold, polypharmacy was categorised as hyperpolypharmacy (≥10 medications), major polypharmacy (5–9 medications) and minor polypharmacy (2–4 medications).

Statistical analysis

Descriptive statistics (frequency and percentages) were used to summarise the categorical variables (sex, marital status, nationality, polypharmacy and co-existing chronic conditions) and means and SD were calculated for continuous variables (age). X^2 tests were utilised to determine the factors associated with adherence and only significant factors were used in the regression models. The factors associated with non-adherence and medication oversupply were assessed using multinomial logistic regression models after adjusting for independent variables (age, gender, nationality, marital status and co-existing chronic conditions). The multinomial logistic regression is an extension of binomial logistic regression to allow for a dependent variable with more than two categories of the outcome measure (eg, good adherence, poor adherence and oversupply). All statistical analyses were conducted using the Statistical Analysis Software V.9.2 and an a priori significance level was set at $p \leq 0.05$.

RESULTS

A total of 5457 patients with T2DM were identified for year 2016 with a majority of them being women (n=3400, 62.3%) and adults 60 years and older (n=2358; 43.2%). More than half of the sample had co-existing chronic conditions, with hypertension (65.6%) and dyslipidaemia (66.0%) being the most common conditions. Around 59.8% of patients had major polypharmacy with 18.7% having hyperpolypharmacy. The average HbA1c was 8.2±1.67. Table 1 presents the demographic and clinical characteristics of the study population. Overall, the vast majority (89.2%) of adults with T2DM were using metformin followed by sitagliptin (23.5%), glibenclamide (16.5%) and pioglitazone (12.1%) (table 2).

OADs adherence

Among the study population, 48.6% had good adherence to OAD (mMPR >0.8 to <1.2), 42.8% had poor adherence (mMPR <0.8) and 8.6% had medication oversupply (mMPR >1.2) (table 1). A significantly higher rate of poor adherence was reported among women when compared with men (45.2% vs 38.9%, p value=0.0001). OADs oversupply was significantly higher among patients with heart failure (24.2%), ischaemic heart disease (16.8%), chronic kidney disease (21.6%), osteoarthritis (12.3%), anxiety

Table 1 Characteristics of the study population and number and row percentage of characteristics by adherence level among adults with diabetes

	Total		Poor adherence mMPR<0.8		Good adherence mMPR>0.8 to <1.2		Medication oversupply mMPR>1.2			
	N	%	N	%	N	%	N	%	P value	Sign.
Total	5457	100.0	2337	42.8	2652	48.6	468.0	8.6		
Age mean (SD)	58.2 (10.8)		57.8 (11.0)		58.5 (10.6)		58.3 (10.8)			
Age groups									0.089	
18–29	39	0.7	15	38.5	20	51.3	4.0	10.3		
30–39	220	4.0	107	48.6	96	43.6	17.0	7.7		
40–49	759	13.9	362	47.7	338	44.5	59.0	7.8		
50–59	2081	38.1	884	42.5	1017	48.9	180.0	8.6		
=>60	2358	43.2	969	41.1	1181	50.1	208.0	8.8		
Marital status									0.099	
Single	480	9.4	186	38.8	244	50.8	50.0	10.4		
Married	4604	90.6	1981	43.0	2242	48.7	381.0	8.3		
Gender									<0.0001	***
Male	2057	37.7	801	38.9	1066	51.8	190.0	9.2		
Female	3400	62.3	1536	45.2	1586	46.6	278.0	8.2		
Nationality									<0.0001	***
Saudi	4830	88.7	2105	43.6	2335	48.3	390.0	8.1		
Non-Saudi	613	11.3	227	37.0	308	50.2	78.0	12.7		
Obesity									0.542	
Yes	437	8.0	180	41.2	223	51.0	34.0	7.8		
No	5020	92.0	2157	43.0	2429	48.4	434.0	8.6		
Hypertension									0.340	
Yes	3581	65.6	1513	42.3	1766	49.3	302.0	8.4		
No	1876	34.4	824	43.9	886	47.2	166.0	8.8		
Dyslipidaemia									0.030	*
Yes	3603	66.0	1556	43.2	1764	49.0	283.0	7.9		
No	1854	34.0	781	42.1	888	47.9	185.0	10.0		
Heart failure									0.005	**
Yes	33	0.6	13	39.4	12	36.4	8.0	24.2		
No	5424	99.4	2324	42.8	2640	48.7	460.0	8.5		
Ischaemic heart disease									<0.0001	***
Yes	161	3.0	67	41.6	67	41.6	27.0	16.8		
No	5296	97.0	2270	42.9	2585	48.8	441.0	8.3		
Chronic kidney disease									0.017	*
Yes	37	0.7	14	37.8	15	40.5	8.0	21.6		
No	5420	99.3	2323	42.9	2637	48.7	460.0	8.5		
Cancer									0.961	
Yes	63	1.2	27	42.9	30	47.6	6.0	9.5		
No	5394	98.8	2310	42.8	2622	48.6	462.0	8.6		
Asthma									0.949	
Yes	571	10.5	244	42.7	276	48.3	51.0	8.9		
No	4886	89.5	2093	42.8	2376	48.6	417.0	8.5		
Osteoarthritis									0.009	**
Yes	373	6.8	140	37.5	187	50.1	46.0	12.3		
No	5084	93.2	2197	43.2	2465	48.5	422.0	8.3		

Continued

Table 1 Continued

	Total		Poor adherence mMPR<0.8		Good adherence mMPR>0.8 to <1.2		Medication oversupply mMPR>1.2			
	N	%	N	%	N	%	N	%	P value	Sign.
Osteoporosis									0.189	
Yes	199	3.6	97	48.7	89	44.7	13.0	6.5		
No	5258	96.4	2240	42.6	2563	48.7	455.0	8.7		
Anxiety									0.001	**
Yes	284	5.2	114	40.1	129	45.4	41.0	14.4		
No	5173	94.8	2223	43.0	2523	48.8	427.0	8.3		
Depression									0.640	
Yes	100	1.8	40	40.0	49	49.0	11.0	11.0		
No	5357	98.2	2297	42.9	2603	48.6	457.0	8.5		
Polypharmacy									<0.0001	***
Hyperpolypharmacy	1019	18.7	387	38.0	494	48.5	138.0	13.5		
Major polypharmacy	3266	59.8	1444	44.2	1584	48.5	238.0	7.3		
Minor polypharmacy	1172	21.5	506	43.2	574	49.0	92.0	7.8		
Average HbA1C mean (SD)	8.2 (1.67)		8.1 (1.67)		8.2 (1.66)		8.3 (1.66)			
Glycaemic control									0.005	**
Good glycaemic control	1231	698	698	46.9	671	45.1	119	8.0		
Poor glycaemic control	4224	1076	1076	41.9	1290	50.2	204	7.9		

Study population comprised of 5457 adults with type 2 diabetes mellitus.
mMPR, modified medication possession ratio; N, number; Sign., significance.
Asterisks (*) represent significant differences based on mMPR from X^2 tests.
***p<0.001; **0.001≤p <0.01; *0.01≤p <0.05.

(14.4%) and depression (11.0%) when compared with those without these comorbid conditions. Medication oversupply was also significantly higher among patients with hyperpolypharmacy when compared with those without polypharmacy (13.5% vs 7.8%, p value =0.0001). The medication oversupply rate was highest for acarbose (17.1%) followed by pioglitazone (15.4%) and glibenclamide (13.9%) (table 2).

OADs adherence and glycaemic control

Results show that good adherence was highest among those who used repaglinide (71.0%) followed by pioglitazone (65.0%) and sitagliptin (59.0%) (table 2). Also, this study found no significant association between medication adherence with any OADs and glycaemic control (table 3). However, a higher rate of good glycaemic

Table 2 Frequency and percentage of OADs and comparison between medication possession ratio, modified (mMPR)

	N	%	Mean adherence	SD	Poor adherence	Good adherence	Oversupply rate
Acarbose	205	3.8	0.97	0.31	24.9%	58.1%	17.1%
Metformin	4869	89.2	0.79	0.31	48.1%	43.3%	8.6%
Glibenclamide	901	16.5	0.93	0.29	29.5%	56.6%	13.9%
Sitagliptin	1285	23.5	0.92	0.27	28.9%	59.9%	11.2%
Repaglinide	46	0.8	0.97	0.21	17.5%	71.7%	10.8%
Pioglitazone	662	12.1	0.97	0.27	19.6%	65.0%	15.4%
Combination	410	7.5	0.84	0.32	46.6%	43.9%	9.5%

Study population comprised of 5457 adults with type 2 diabetes mellitus.
mMPR, modified medication possession ratio; N, number; OADs, oral antidiabetic drugs.

Table 3 Association between adherence to OADs and glycaemic control

	Good glycaemic control		Poor glycaemic control				
	N	%	N	%	X^2	P value	Sig
Adherence to diabetic medications							
Acarbose					0.912	0.634	
Poor adherence	7	20	28	80			
Good adherence	15	17.6	70	82.4			
Oversupply	3	11.1	24	88.9			
Metformin					0.978	0.613	
Poor adherence	698	39.2	1084	60.8			
Good adherence	601	38	980	62			
Oversupply	113	40.8	164	59.2			
Glibenclamide					0.151	0.927	
Poor adherence	35	15.4	193	84.6			
Good adherence	68	15.7	366	84.3			
Oversupply	15	14.2	91	85.8			
Sitaglibtin					0.188	0.91	
Poor adherence	50	19.5	206	80.5			
Good adherence	97	18.3	433	81.7			
Oversupply	18	18.2	81	81.8			
Repaglinide					0.625	0.732	
Poor adherence	2	25	6	75			
Good adherence	5	20	20	80			
Oversupply	0	0	2	100			
Pioglitazone					0.52	0.771	
Poor adherence	19	17.4	90	82.6			
Good adherence	70	20.3	275	79.7			
Oversupply	14	21.2	52	78.8			
Combination therapy					5.928	0.052	
Poor adherence	22	15.8	117	84.2			
Good adherence	30	23.6	97	76.4			
Oversupply	8	36.4	14	63.6			

Study population comprised of 5457 Adults with type 2 diabetes mellitus.
OADs: oral antidiabetic drugs; Sig., significance.

control (HbA1C<7%) was observed among patients on metformin (24.1%) followed by combination therapy (12.0%) and pioglitazone (11.5%).

Factors associated with OADs adherence

The adjusted OR (AOR) and 95% CI from multinomial logistic regressions on adherence to OADs are presented in table 4. Several factors associated with OADs adherence were identified: gender, nationality, co-existing chronic conditions and polypharmacy. Women with T2DM were less likely to have good adherence (AOR=0.76, 95% CI=0.67, 0.86) compared with men. Medication oversupply was more likely among T2DM patients with hyperpolypharmacy (AOR=1.88, 95% CI=1.36, 2.63), comorbid osteoarthritis (AOR=1.72, 95% CI=1.20, 02.45) and non-Saudi patients (AOR=1.53, 95% CI=1.16, 2.01).

DISCUSSION

Medication adherence

Medication adherence is critical in the treatment of patients with diabetes. Failure to adhere to prescribed medication regimen is recognised as a serious issue resulting in negative consequences to the patient and the healthcare system as well. Thus, there is a need to identify specific barriers that will help in adapting appropriate tools to overcome and improve medication adherence.[35 42]

Table 4 OR and 95% CIs from multinomial logistic regression on adherence among adults with type 2 diabetes mellitus

	Good adherence				Medication oversupply			
	OR	95% CI	P value	Sig.	OR	95% CI	P value	Sig.
Last HbA1C								
Good<7%	0.81	(0.70 to 1.10)	0.004		0.90	(0.69 to 1.17)	0.434	
Poor>7%								
Gender								
Female	0.76	(0.67 to 0.86)	<0.0001	***	0.64	(0.49 to 0.83)	0.001	**
Male (Ref.)								
Nationality								
Non-Saudi	1.15	(0.93 to 1.43)	0.218		1.53	(1.16 to 2.01)	0.023	*
Saudi (Ref.)								
Ischaemic heart disease								
Yes	0.78	(0.48 to 1.28)	0.215		1.37	(0.99 to 2.80)	0.287	
No (Ref.)								
Heart failure								
Yes	0.78	(0.34 to 1.71)	0.446		1.77	(0.79 to 4.47)	0.343	
No (Ref.)								
Dyslipidaemia								
Yes	1.06	(0.94 to 1.21)	0.683		0.83	(0.69 to 1.02)	0.270	
No (Ref.)								
CKD								
Yes	0.78	(0.42 to 1.81)	0.756		1.97	(0.79 to 4.48)	0.089	
No (Ref.)								
Osteoarthritis								
Yes	1.15	(0.92 to 1.81)	0.260		1.72	(1.20 to 2.45)	0.008	**
No (Ref.)								
Anxiety								
Yes	0.89	(0.64 to 1.25)	0.888		1.41	(0.95 to 2.08)	0.072	
No (Ref.)								
Polypharmacy								
Hyperpolypharmacy	1.11	(0.86 to 1.41)	0.176		1.88	(1.36 to 2.63)	0.006	**
Major polypharmacy	1.04	(0.87 to 1.23)	0.459		1.27	(0.98 to 1.64)	0.871	
Minor polypharmacy (Ref.)								

Asterisks (*) represent significant differences based on adherence from multinomial logistic regressions with poor adherence as the reference group.
***p<.001; **.001≤p <.01; *.01≤p <.05
Study population comprised of 5457 adults with type 2 diabetes mellitus.
CKD, chronic kidney disease; HbA1C, glycated haemoglobin; Ref., reference group; Sig., significance.

The heterogeneity, complexity and importance of this issue have been extensively studied and well recognised in the literature.[35 43 44] Several barriers and facilitators of adherence have been identified including patient-related factors (belief and knowledge, cognitive function, health literacy), physician-related factors (communication with patient), medication-related factors (adverse drug reaction, drug regimen complexity, cost) and system-based factors (lack of medication review, lack of patient follow-up).[43 45] However, factors associated with non-adherence were not comprehensive and are reported to vary depending on the nature of the disease (eg, severity), patients' characteristics (eg, demographic and socioeconomic status).[46] To explore the issue of medication non-adherence in patients with T2DM in Saudi Arabia, this study utilised patients' refill data from EHRs of a tertiary hospital and estimated patients' overall adherence to OADs using mMPR values. The study found that almost half of the study population with T2DM had good adherence (mMPR >0.8). In the published

literature, good adherence has been shown to vary widely and results from a systematic review of 20 retrospective studies demonstrated that adherence to OADs therapy ranged from 36% to 93% in patients with diabetes.[47] These variations in adherence were affected by several factors including the adherence measurement tools, population or institution where the studies were conducted, and the medications included in the studies.[44]

The study findings also revealed that adherence varied widely across different medications with the highest adherence rates observed in patients on repaglinide followed by pioglitazone users and was lowest among metformin users. Several studies have demonstrated that patients on pioglitazone and sulfonylureas have a greater adherence rate than those on metformin.[48] The side effects of metformin such as flatulence and diarrhoea can possibly be the cause of poor adherence rates among patients.[49] In this study, women were less likely to be adherent as compared with men, which was not consistent with previous studies that showed women having significantly higher adherence rates than men.[50–52] However, few studies have demonstrated similar surprising findings in which women have low level of adherence.[53–55] Some reason reported in the literature indicated that women often prescribed more medication, have a complex medications regimen and experience more side effects which could contribute to lower rates of adherence.[56] Although the actual reason behind these differences in adherence level between men and women warrants further investigation, these differences should be considered in personalised treatment plan in order to improve adherence rate and clinical outcomes.[56]

Medication oversupply

Another interesting study finding was related to medication oversupply; around 8.6% of the patients had medication oversupply, in particular, among those with chronic kidney disease and patients with hyperpolypharmacy. In addition to the significant economic burden associated with excessive supply of medications, oversupply of diabetes medications may result in accidental medication errors, which can possibly lead to negative outcomes.[57] The current study results are consistent with the published studies that reported medication oversupply range from 6.7% to 13.4%.[23 58] Medication oversupply could be a result of a number of factors such as sicker patients, medication management system issues, poor medication reconciliation, patients visiting multiple clinicians and miscommunication between the patients and their clinicians.[25 58] It should be noted that KSUMC utilises a 90-day supply for chronic disease, which has been previously reported as being more convenient to the patient and can improve patient adherence. However, it can also increase the chance of the patient having an excess amount of medication, which can lead to oversupply and wastage. This is especially the case when the treatment regimen of a patient has been switched or changed.[58 59]

Relationship between adherence to OADs and glycaemic control

There is compelling data to show that glycaemic control is essential in the management of T2DM and it dramatically reduces diabetes-related complications. In the UK Prospective Diabetes Study (UKPDS) trial, the microvascular complication rate was reduced by 25% and myocardial infarction (MI) by 16% in the intensive treatment arm.[60] A meta-analysis of the four diabetes trials, Action to Control Cardiovascular Risk in Diabetes, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, UKPDS and Veterans Affairs Diabetes Trial, showed a 15% reduction of relative risk in non-fatal MI with every 1% decrease in HbA1c.[61] A retrospective cohort study reported that medication adherence was associated with better glycaemic control by one and a half folds when compared with non-adherent patients.[62] Not surprisingly, poor adherence to OADs was associated with poor glycaemic control as documented by many published studies.[63 64] This study reported that around two-thirds of patients with T2DM failed to achieve adequate glycaemic control, which is consistent with another published study in Saudi Arabia,[65] but had higher than the average global HbA1c levels reported in the literature (45%).[66] However, no significant association between achieving glycaemic control and adherence level was seen in this study.

Poor glycaemic control due to non-adherence to OADs can lead to higher microvascular complications (ie, nephropathy, retinopathy, and neuropathy),[67] higher macrovascular complications (ie, MI and ischaemic stroke)[68] and high risk of mortality,[68] hospitalisation and emergency department visits.[16] Besides, poor glycaemic control due to non-adherence to OADs can lead to an increased diabetes care cost. In the USA, non-adherence to diabetes medications cost $337 billion in 2013.[17 18] In Saudi Arabia, the economic burden of T2DM compliance and persistence for patients who struggle to achieve optimal therapy is estimated around 3.9 billion Saudi Riyals (US$1.04 billion) and the cost is expected to significantly increase in the future.[69] The value of adherence to pharmacologic treatments in achieving and controlling diabetes has clearly been established. Good adherence can mitigate the risk of hospitalisation, emergency room visits,[70] all-cause mortality[71] and could improve the overall glycaemic control.[15 16 72]

Strengths and limitations

Adherence can be measured by different methodological approaches. In this study, adherence was assessed using the mMPR method, which is a reliable method and depends on real-world data obtained from patient's medication refill history. This method can be used for a large population at a relatively low cost and also prevents recall bias, which is associated with patient interview-based adherence methods. This study sheds some light into concomitant diseases that were associated with OADs non-adherence. Although the current study provides

real-world information from more than 5400 patients about adherence rate to different OADs and the relationship of OADs and glycaemic control, few limitations were observed. The study population was mostly patients who attended the KSUMC in central Saudi Arabia; therefore, it is difficult to extrapolate the study findings to the whole Saudi population residing in the other geographical areas of the country. Nevertheless, patients included in this study represent almost all Saudi citizens and expatriate groups living in Saudi Arabia. In addition, important information, such as health literacy, educational level, economic status, marital status, knowledge about disease and medications thatmight be contributing factors to medication non-adherence, was not available from EHRs. It should be noted that the adherence in this study was based on pharmacy refills data, which only indicates the possession of the medication, but does not capture the actual consumption of the medication by the patient. This is one of the limitations in calculating adherence using pharmacy refills data as it assumes that the medication was actually taken by the patient, which may not necessarily be the case. The main advantage of using the EHRs is the availability of large sample size that can provide precise estimates and availability of dispensing date and quantity dispensed, which is hard to collect from the patients using the patient-reported measures. Other tools that potentially provide more accurate estimation about the actual consumption and adherence include direct measures such as measurement of drug of metabolite in body fluids or testing for biomarkers. However, these are expensive and intrusive to patients and therefore difficult to implement.

Future implications

Healthcare professionals have to pay special attention to patients with diabetes, especially those with polypharmacy and concomitant diseases, as this will increase the risk for non-adherence to OADs medication. Although we have few patients with medication oversupply in our study, it is worthwhile for healthcare providers and policymakers to be aware of this important issue and to plan for a strategy to prevent both under/over-supply of medications. Further investigations are needed to explore the oversupply across different populations and chronic diseases as the rate could vary significantly. This will allow the estimation of financial loss due to medication oversupply (eg, wastage) and can help implement effective strategies to prevent medication oversupply. In addition, our findings indicated a surprising result regarding the adherence in female with OADs in patient with T2DM, thereby identifying a need to investigate the factors affecting adherence to OADs among females.

Clinical practice implications

Healthcare providers must remain vigilant when evaluating adherence to OADs medications, by counselling patients at each visit and properly assessing medication adherence as a behaviour. Improving patient-clinician relationships, providing information to guide self-management to support patients with diabetes can provide a clinically significant improvement in glycaemic control for some patients and improve other health outcomes. As medication oversupply was an issue in our study especially among those with comorbid chronic conditions and those with multiple medications, pharmacy services such as reconciliation and medication therapy management are needed to optimise medication use.

CONCLUSIONS

The study findings support the growing concern of non-adherence to OADs among patients with T2DM in Saudi Arabia. Both providers and pharmacists, in their interaction with the patients, should stress on the importance of adherence and its impact on clinical, economic and humanistic outcomes and also focus on preventive measures such as lifestyle modifications. Decision makers have to invest in behavioural interventions such as motivational interviewing, planned behaviour education and problem-solving training which can boost the adherence rates to medications and reduce medication oversupply.[73] This is particularly important in patients with polypharmacy or hyperpolypharmacy and high burden of comorbid conditions.

Author affiliations
[1]Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[2]Drug Sector, Saudi Food and Drug Authority, Riyadh, Riyadh, Saudi Arabia
[3]Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[4]Department of Clinical Pharmacy, College of Pharmacy, University of Hail, Hail, Saudi Arabia
[5]Department of Clinical and Hospital Pharmacy, College of Pharmacy, Taibah University, Madinah, Saudi Arabia
[6]Investigational Drugs and Research Unit, King Khalid University Hospital, Riyadh, Saudi Arabia
[7]Division of Pharmaceutical, Administrative and Social Sciences, Duquesne University School of Pharmacy, Pittsburgh, USA

Acknowledgements The project was fully supported financially by the Vice Deanship of Research Chairs, King Saud University, Riyadh, Saudi Arabia.

Contributors BB, MA, NA and TMA participated in designing the study. SA and MM reviewed the proposal and obtained ethical approval. BB and MA did the statistical analysis. BB, MA, TA, TMA and KMK contributed to the interpretation of the results. All authors drafted, revised and approved the final version of this manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the institutional review board under protocol number (E-16-2203).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No data are available.

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014;37(Supplement 1):S81–S90.
2. Ogurtsova K, da Rocha Fernandes JD, Huang Y, *et al*. IDF Diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 2017;128:40–50.
3. Federation ID. *IDF Diabetes atlas*. 8th edn. Middle East and North Africa, 2017.
4. Al-Daghri NM, Al-Attas OS, Alokail MS, *et al*. Diabetes mellitus type 2 and other chronic non-communicable diseases in the central region, Saudi Arabia (Riyadh cohort 2): a decade of an epidemic. *BMC Med* 2011;9:76.
5. Guariguata L, Whiting DR, Hambleton I, *et al*. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* 2014;103:137–49.
6. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
7. Organization WH. Diabetes country profiles 2016. 2016 http://www.who.int/diabetes/country-profiles/sau_en.pdf?ua=1.
8. Collins AJ, Foley RN, Gilbertson DT, *et al*. United States renal data system public health surveillance of chronic kidney disease and end-stage renal disease. *Kidney Int Suppl* 2015;5:2–7.
9. Moxey PW, Gogalniceanu P, Hinchliffe RJ, *et al*. Lower extremity amputations--a review of global variability in incidence. *Diabet Med* 2011;28:1144–53.
10. Yau JW, Rogers SL, Kawasaki R, *et al*. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35:556–64.
11. Sarwar N, Gao P, Seshasai SR, *et al*. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215–22.
12. Bommer C, Heesemann E, Sagalova V, *et al*. The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study. *Lancet Diabetes Endocrinol* 2017;5:423–30.
13. Alhowaish AK. Economic costs of diabetes in Saudi Arabia. *J Family Community Med* 2013;20:1.
14. Mokdad AH, Tuffaha M, Hanlon M, *et al*. Cost of diabetes in the Kingdom of Saudi Arabia, 2014. *J Diabetes Metab* 2015;6:2.
15. Ho PM, Rumsfeld JS, Masoudi FA, *et al*. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med* 2006;166:1836–41.
16. Lin LK, Sun Y, Heng BH, *et al*. Medication adherence and glycemic control among newly diagnosed diabetes patients. *BMJ Open Diabetes Res Care* 2017;5:e000429.
17. Egede LE, Gebregziabher M, Dismuke CE, *et al*. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. *Diabetes Care* 2012;35:2533–9.
18. Kennedy-Martin T, Boye KS, Peng X. Cost of medication adherence and persistence in type 2 diabetes mellitus: a literature review. *Patient Prefer Adherence* 2017;11:1103–17.
19. García Díaz E, Ramírez Medina D, García López A, *et al*. Determinants of adherence to hypoglycemic agents and medical visits in patients with type 2 diabetes mellitus. *Endocrinol Diabetes Nutr* 2017;64:531–8.
20. Khan AR, Al-Abdul Lateef ZN, Al Aithan MA, *et al*. Factors contributing to non-compliance among diabetics attending primary health centers in the Al Hasa district of Saudi Arabia. *J Family Community Med* 2012;19:26.
21. Chaiyakunapruk N, Thanarungroj A, Cheewasithirungrueng N, *et al*. Estimation of financial burden due to oversupply of medications for chronic diseases. *Asia Pac J Public Health* 2012;24:487–94.
22. Evans JM, Donnan PT, Morris AD. Adherence to oral hypoglycaemic agents prior to insulin therapy in Type 2 diabetes. *Diabet Med* 2002;19:685–8.
23. Dilokthornsakul P, Chaiyakunapruk N, Nimpitakpong P, *et al*. Understanding medication oversupply and its predictors in the outpatient departments in Thailand. *BMC Health Serv Res* 2014;14:408.
24. Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. *Diabetes Care* 2004;27:2149–53.
25. Stroupe KT, Murray MD, Stump TE, *et al*. Association between medication supplies and healthcare costs in older adults from an urban healthcare system. *J Am Geriatr Soc* 2000;48:760–8.
26. Stroupe KT, Teal EY, Weiner M, *et al*. Health care and medication costs and use among older adults with heart failure. *Am J Med* 2004;116:443–50.
27. Kim N, Agostini JV, Justice AC. Refill adherence to oral hypoglycemic agents and glycemic control in veterans. *Ann Pharmacother* 2010;44:800–8.
28. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487–97.
29. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 1999;21:1074–90. Discussion 3.
30. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;119:3028–35.
31. Jimmy B, Jose J. Patient medication adherence: measures in daily practice. *Oman Med J* 2011;26:155–9.
32. Gordon J, McEwan P, Idris I, *et al*. Treatment choice, medication adherence and glycemic efficacy in people with type 2 diabetes: a UK clinical practice database study. *BMJ Open Diabetes Res Care* 2018;6:e000512.
33. Lawrence DB, Ragucci KR, Long LB, *et al*. Relationship of oral antihyperglycemic (sulfonylurea or metformin) medication adherence and hemoglobin A1c goal attainment for HMO patients enrolled in a diabetes disease management program. *J Manag Care Pharm* 2006;12:466–71.
34. Rozenfeld Y, Hunt JS, Plauschinat C, *et al*. Oral antidiabetic medication adherence and glycemic control in managed care. *Am J Manag Care* 2008;14:71–5.
35. Capoccia K, Odegard PS, Letassy N. Medication adherence with diabetes medication: a systematic review of the literature. *Diabetes Educ* 2016;42:34–71.
36. Raebel MA, Schmittdiel J, Karter AJ, *et al*. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care* 2013;51(8):S11–21.
37. Hess LM, Raebel MA, Conner DA, *et al*. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother* 2006;40(7-8):1280–8.
38. American Diabetes Association. Standards of medical care in diabetes--2014. *Diabetes Care* 2014;37(Supplement 1):S14–80.
39. Teljeur C, Smith SM, Paul G, *et al*. Multimorbidity in a cohort of patients with type 2 diabetes. *Eur J Gen Pract* 2013;19:17–22.
40. Iglay K, Hannachi H, Joseph Howie P, *et al*. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. *Curr Med Res Opin* 2016;32:1243–52.
41. Monégat M, Sermet C, Perronnin M, *et al*. Polypharmacy: definitions, measurement and stakes involved: review of the literature and measurement tests. *Quest d'économie la santé* 2014;204:1–8.
42. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. *Am J Geriatr Pharmacother* 2011;9:11–23.
43. Yap AF, Thirumoorthy T, Kwan YH. Systematic review of the barriers affecting medication adherence in older adults. *Geriatr Gerontol Int* 2016;16:1093–101.
44. Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. *Diabet Med* 2015;32:725–37.
45. Mathes T, Jaschinski T, Pieper D. Adherence influencing factors - a systematic review of systematic reviews. *Arch Public Health* 2014;72:37.
46. Jaam M, Ibrahim MIM, Kheir N, *et al*. Factors associated with medication adherence among patients with diabetes in the Middle East and North Africa region: a systematic mixed studies review. *Diabetes Res Clin Pract* 2017;129:1–15.
47. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004;27:1218–24.
48. Hansen RA, Farley JF, Droege M, *et al*. A retrospective cohort study of economic outcomes and adherence to monotherapy with metformin, pioglitazone, or a sulfonylurea among patients with type 2 diabetes mellitus in the United States from 2003 to 2005. *Clin Ther* 2010;32:1308–19.
49. McGovern A, Hinton W, Calderara S, *et al*. A class comparison of medication persistence in people with Type 2 diabetes: a retrospective observational study. *Diabetes Ther* 2018;9:229–42.
50. Parada H, Horton LA, Cherrington A, *et al*. Correlates of medication nonadherence among Latinos with type 2 diabetes. *Diabetes Educ* 2012;38:552–61.
51. Cohen HW, Shmukler C, Ullman R, *et al*. Measurements of medication adherence in diabetic patients with poorly controlled HbA(1c). *Diabet Med* 2010;27:210–6.
52. Wong MC, Kong AP, So WY, *et al*. Adherence to oral hypoglycemic agents in 26,782 Chinese patients: a cohort study. *J Clin Pharmacol* 2011;51:1474–82.

53. Mahmoud MIH. Compliance with treatment of patients with hypertension in Almadinah Almunawwarah: a community-based study. *Journal of Taibah University Medical Sciences* 2012;7:92–8.
54. Khayyat SM, Khayyat SM, Hyat Alhazmi RS, *et al*. Predictors of medication adherence and blood pressure control among Saudi Hypertensive patients attending primary care clinics: a cross-sectional study. *PLoS One* 2017;12:e0171255.
55. Khalil SA, Elzubier AG. Drug compliance among hypertensive patients in Tabuk, Saudi Arabia. *J Hypertens* 1997;15:561–5.
56. Manteuffel M, Williams S, Chen W, *et al*. Influence of patient sex and gender on medication use, adherence, and prescribing alignment with guidelines. *J Womens Health* 2014;23:112–9.
57. Chen CC, Blank RH, Cheng SH. Medication supply, healthcare outcomes and healthcare expenses: longitudinal analyses of patients with type 2 diabetes and hypertension. *Health Policy* 2014;117:374–81.
58. Thorpe CT, Johnson H, Dopp AL, *et al*. Medication oversupply in patients with diabetes. *Res Social Adm Pharm* 2015;11:382–400.
59. Domino ME, Martin BC, Wiley-Exley E, *et al*. Increasing time costs and copayments for prescription drugs: an analysis of policy changes in a complex environment. *Health Serv Res* 2011;46:900–19.
60. Genuth S, Eastman R, Kahn R, *et al*. Implications of the United kingdom prospective diabetes study. *Diabetes Care* 2003;26:S28–32.
61. Turnbull F, Abraira C, Anderson R, *et al*. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Springer* 2009.
62. McAdam-Marx C, Bellows BK, Unni S, *et al*. Impact of adherence and weight loss on glycemic control in patients with type 2 diabetes: cohort analyses of integrated medical record, pharmacy claims, and patient-reported data. *J Manag Care Spec Pharm* 2014;20:691–700.
63. Vichayanrat A, Matawaran BJ, Wibudi A, *et al*. Assessment of baseline characteristics, glycemic control and oral antidiabetic treatment in Asian patients with diabetes: the registry for assessing OAD usage in diabetes management (REASON) Asia study. *J Diabetes* 2013;5:309–18.
64. Feldman BS, Cohen-Stavi CJ, Leibowitz M, *et al*. Defining the role of medication adherence in poor glycemic control among a general adult population with diabetes. *PLoS One* 2014;9:e108145.
65. Rabba AK, Aljiris WS, Ahmed NJ, *et al*. Medication adherence in type 2 diabetic patients: a study in Saudi Arabia. 2017.
66. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. *Patient Prefer Adherence* 2016;10:1299–307.
67. Fukuda H, Mizobe M. Impact of nonadherence on complication risks and healthcare costs in patients newly-diagnosed with diabetes. *Diabetes Res Clin Pract* 2017;123:55–62.
68. Gatwood JD, Chisholm-Burns M, Davis R, *et al*. Differences in health outcomes associated with initial adherence to oral antidiabetes medications among veterans with uncomplicated Type 2 diabetes: a 5-year survival analysis. *Diabet Med* 2018;35:1571–9.
69. IMS Institute for Healthcare Informatics. Improving Type 2 Diabetes therapy compliance and persistence in the Kingdom of Saudi Arabia. 2016.
70. Roebuck MC, Kaestner RJ, Dougherty JS. Impact of medication adherence on health services utilization in medicaid. *Med Care* 2018;56:1–73.
71. Simard P, Presse N, Roy L, *et al*. Association between metformin adherence and all-cause mortality among new users of metformin: a nested case-control study. *Ann Pharmacother* 2018;52:305–13.
72. Schectman JM, Nadkarni MM, Voss JD. The association between diabetes metabolic control and drug adherence in an indigent population. *Diabetes Care* 2002;25:1015–21.
73. Kini V, Ho PM. Interventions to improve medication adherence: a review. *JAMA* 2018;320:2461–73.