Polypharmacy among patients with diabetes: a cross-sectional retrospective study in a tertiary hospital in Saudi Arabia

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Abstract Patients with diabetes are at high risk for polypharmacy (ie, use of multiple medications) for treatment of diabetes, associated comorbidities and other coexisting conditions. This study aims to estimate the prevalence of polypharmacy and factors associated with polypharmacy among adult patients with diabetes.

Methods A cross-sectional retrospective observational study of adults with diabetes, who visited the outpatient clinic of a tertiary teaching hospital in Saudi Arabia, was conducted. Data were extracted from the Electronic Health Record database for a period of 12 months (January–December 2016). Polypharmacy was defined as the cumulative use of five or more medications. Polypharmacy among adults with diabetes was measured by calculating the average number of medications prescribed per patient. A multivariable logistic regression model was used to examine the factors associated with polypharmacy.

Results A total of 8932 adults with diabetes were included in this study. Of these, nearly 78% had polypharmacy which was more likely among women as compared with men and more likely among older adults (age ≥60 years) as compared with the adults. Also, polypharmacy was two times as likely among patients with coexisting cardiovascular conditions (adjusted OR=2.89; 95% CI 2.54 to 3.29), respiratory disease (AOR=2.42; 95% CI 1.92 to 3.03) and mental health conditions (AOR=2.19; 95% CI 1.74 to 2.76), and three times as likely among patients with coexisting musculoskeletal disease (AOR=3.16; 95% CI 2.31 to 4.30) as compared with those without these coexisting chronic conditions categories.

Conclusions Polypharmacy is common among patients with diabetes, with an even higher rate in older adults patients. Healthcare providers can help in detecting polypharmacy and in providing recommendations for simplifying medication regimens and minimising medications to enhance the outcome of diabetes care.

INTRODUCTION Diabetes is a highly prevalent chronic condition among adults in Saudi Arabia; between 21% and 24% of adults are estimated to have diabetes.1,2 It is projected that 27% of adults in Saudi Arabia will have diabetes by 2035.3 Diabetes is 1 of the top 10 causes of morbidity and mortality worldwide.4 Patients with diabetes often have coexisting chronic health conditions such as hypertension, dyslipidaemia, coronary artery disease, depression and chronic kidney disease, which requires the use of multiple medications to treat those coexisting chronic conditions.5 All of this put patients with diabetes at high risk of polypharmacy,6 7 with an estimated prevalence of 57%–84% of patients with diabetes using five or more medications.8 A study among adults with diabetes in the USA documented that the 54% of adults with diabetes have polypharmacy.9 A multicentre cross-sectional survey conducted in Italy reported that 57% of patients with diabetes use five or more medications.10 In addition, polypharmacy was reported among 84% older adults patients with diabetes.8 In Saudi Arabia, a cross-sectional study among 766 adults who visited outpatient’s clinic at a tertiary care centre,
reported that the prevalence of polypharmacy among patients with diabetes was 71%.11

An examination of polypharmacy among patients with diabetes is important because polypharmacy increases the probability of the adverse drug events,12 13 drug-drug interactions,14 duplication of therapy,15 decreases compliance to antidiabetic medications16 and leads to suboptimal glycaemic control.17 The presence of polypharmacy is also associated with prescribing cascade, in which adverse drug events are misinterpreted as new medical conditions which can result in the prescription of new medications to treat those conditions.18 Polypharmacy has other negative health consequences such as increased risk of hospitalisation and medication error,19 20 higher risk of fall,21 poor functional status,22 poor quality of life and high healthcare cost.23 24 Polypharmacy among patients with diabetes is often associated with many factors. These include age,11 sex,10 coexisting conditions,10 rurality,11 25 diabetes complications10 and aggressive diabetes treatment.26 27

To date, limited studies have examined the prevalence of polypharmacy among adults with diabetes living in Saudi Arabia on a large scale, and assessed the specific factors that put patients at risk of polypharmacy. Identifying the prevalence and the subgroup of patients at high risk of polypharmacy will facilitate pharmacovigilance efforts in clinical practice settings. Therefore, the primary objective of this observational study is to examine the prevalence of polypharmacy among adults with diabetes in Saudi Arabia and to identify the factors that are associated with polypharmacy, specifically the association between coexisting chronic conditions and polypharmacy.

METHODS

Study design

A cross-sectional retrospective observational study was conducted in a tertiary teaching hospital in Saudi Arabia. This hospital is one of the largest tertiary teaching hospitals in Riyadh, Saudi Arabia, with a 1200-bed facility and all general and subspecialty medical services. The hospital provides primary, secondary and tertiary care services. The patient population is composed predominantly of local citizens as well as residents, from Northern region in Riyadh; the hospital also serves the entire country as a referral centre.

Data source and data extraction

This study used data retrieved from the Electronic Health Record (EHR) database for the period from 1 January 2016 to 30 December 2016. Strict confidentiality of the data was maintained throughout the research process. The data from EHR were derived from demographics file, clinical diagnosis file and prescription drug file. The demographics file contained information about the patients’ date of birth, gender, marital status, nationality and encounter type. The clinical diagnosis file provided information about the clinical diagnosis from inpatient and outpatient visits. Physicians reported clinical diagnosis using the International Classifications of Diseases, ninth edition, Clinical Modification (ICD-9-CM) codes, ICD-10th edition, CM codes or the Systematised Nomenclature of Medicine diagnosis codes. The prescription drug file contained information about the medications used. The demographics, clinical diagnosis and prescription drug files were merged into one file using the encrypted patient medical record number. The completeness and the validity of the data from EHR in this tertiary teaching hospital in Saudi Arabia has not been studied before; however, the researchers of this study examined the completeness of this data and found that 91.0% of the patients had a complete data (ie, have information on the age, gender, marital status, nationality, encounter type and clinical diagnosis) and 85.0% of the patients had complete medication-related information.

Study population

The study population comprised all adult patients with diabetes (type 1 and type 2) (age ≥18 year) (n=8932) who received their treatment at the outpatient’s setting in the tertiary teaching hospital during a 1-year period. No exclusion criteria were applied to the study population.

Patient and public involvement

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

Measures

Dependent variable

In our study, the dependent variable was ‘polypharmacy’. There are different approaches in the literature to measure polypharmacy such as simultaneous, cumulative and continuous. Also, there is no consensus on the thresholds regarding the number of medications above which we consider the existence of polypharmacy.28 In the current study, we defined polypharmacy as the cumulative use of five or more medications during a 1-year period, this threshold has been used more than others.25 28 29 Using this definition, the prevalence of polypharmacy among adults was measured by the sum of unique therapeutic counter (OTC) medications categories were included in our definition of polypharmacy.

Independent variables

Independent variables included were age groups in years (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, >80), gender, nationality (Saudi, non-Saudi), marital status (married, unmarried) and documented chronic conditions which were classified into five categories (cardiovascular, chronic kidney disease, musculoskeletal, respiratory or mental health conditions) (online supplementary appendix 1). Cardiovascular conditions comprised of hypertension, ischaemic heart disease, vascular heart disease, stroke,
heart failure and dyslipidaemia. Musculoskeletal conditions composed of osteoarthritis and osteoporosis; respiratory conditions include asthma and chronic obstructive pulmonary disease (COPD). Mental health conditions include dementia, depression, anxiety and schizophrenia. These conditions have been selected because they are highly prevalent among patients with diabetes and some of them were associated with polypharmacy.5 30

Statistical analysis
Frequency and percentage were used to describe the categorical variables (age, sex, marital status, nationality, coexisting chronic conditions and polypharmacy). Mean and SD were used to describe continuous variables. χ² tests were used to examine the factors associated with polypharmacy. A multivariable logistic regression was used to examine the factors associated with polypharmacy (ie, use of ≥5 medications) after adjusting for age, sex, marital status, nationality and coexisting chronic conditions. All statistical analyses were carried out using the SAS V.9.2.

RESULTS
A total of 8932 adult patients were identified during the 12-month period. The majority were Saudi (89.4%), female (62.2%) and 43.3% of the study population were older adults (age ≥60 years), the mean age of the study population was 57 years old. About half of the subjects (54.1%) had two or more diagnosed coexisting chronic health conditions. Hypertension, dyslipidaemia, asthma, osteoarthritis and anxiety were among the most common chronic conditions in our study population. Characteristics of the study population are presented in table 1.

Polypharmacy among patients with diabetes
Overall, 77.9% of adults with diabetes have used (cumulative) five or more medications. Also, when we identified the rate of hyperpolypharmacy (ie, taking 10 or more medications), we found that 17.2% of adults have a hyperpolypharmacy. The most commonly used medications in our study population were antidiabetic medications (81.4%), followed by non-steroidal anti-inflammatory drugs (NSAIDs) (72.4%) and antihyperlipidaemic agents (68.8%) (table 2).

The study population characteristics by polypharmacy status are summarised in table 1. This study found a significantly higher percentage of polypharmacy among older adults as compared with patients with age between 18 and 29 years (84.8% vs 37.4%, p<0.001). Women with diabetes had a significantly higher percentage of polypharmacy as compared with men (81.7% vs 71.6%, p<0.001). Moreover, polypharmacy was significantly higher among patients with diabetes with two or more coexisting comorbid conditions versus those with no coexisting chronic conditions (89.6% vs 48.6%, p<0.001). Looking at comorbid conditions closely, polypharmacy was significantly higher among patients with cardiovascular disease (83.4%, p<0.001), chronic kidney disease (95.2%, p<0.001), musculoskeletal (93.6%, p<0.001), respiratory (89.0%, p<0.001) and mental health conditions (85.4%, p<0.001) as compared with those without those coexisting chronic conditions.

Logistic regression: factors associated with polypharmacy
The adjusted ORs (AORs) and 95% CIs from multivariable logistic regression on polypharmacy are displayed in table 3. Several factors were identified: age, gender and coexisting chronic conditions. Polypharmacy was more likely among older adults as compared with younger adults. Women were more likely to have polypharmacy compared with men (AOR=1.60; 95% CI 1.43 to 1.79). Cardiovascular diseases, mental conditions, respiratory and musculoskeletal diseases were all significantly associated with polypharmacy. For example, adults with diabetes and musculoskeletal disease were three times more likely to have polypharmacy (AOR=3.16; 95% CI 2.31 to 4.30) as compared with adults with diabetes and without musculoskeletal conditions.

DISCUSSION
Our study was set out to examine the prevalence of polypharmacy among adults with diabetes in Saudi Arabia. In this large sample of subjects with diabetes, the rate of polypharmacy was high, as nearly four out of five adults with diabetes were prescribed five or more medications. Similar rates were reported in the literature among patients with diabetes 54%–84%.8–10 however, to our knowledge, no study has attempted to measure the rate of polypharmacy among all age groups of adults with diabetes, which is a major contribution of our study. A higher rate of polypharmacy among older individuals (age 60 and above) as compared with all age groups was also observed in this study. Studies among adults in the general population have reported that older adults (defined as age ≥60 or age ≥65 years) have a higher risk of polypharmacy use as compared with adults.11 32 One possible reason for the high rate of polypharmacy among this population is the coexistence of other chronic conditions.

Furthermore, a noteworthy finding of the current study is the high prevalence of chronic conditions and the higher rate of polypharmacy among diabetic individuals with coexisting chronic conditions. Previous studies have shown that 90% of patients with diabetes had at least one coexisting chronic condition.5 our study found that 86% of patients with diabetes had at least one coexisting chronic condition. It is plausible that the high rate of polypharmacy in this study is potentially associated with the number of comorbidities among the study population. The findings of this study support that patients with diabetes with multiple chronic conditions were at higher risk of polypharmacy.5 33 Although there is a well-documented literature on the relationship between the higher number of coexisting conditions and polypharmacy,5 10 34 our study extended the literature by analysing the association between the type of chronic conditions.
Table 1  Characteristics of the study population number and row percentage of characteristics by polypharmacy among adults with diabetes, Electronic Health Records database, 2016

|                        | Total | Polypharmacy | No polypharmacy | X² value | Significance |
|------------------------|-------|--------------|-----------------|----------|--------------|
|                        | N     | %            | N               | %        | N            | %           |          |
| Total                  | 8932  | 100.0        | 6957            | 77.9     | 1975         | 22.1        |          |
| # of medications mean(SD) | 6.54 (3.50) | 8.06 (2.97) | 2.85 (1.14)     |          |              |              |          |
| Age mean (SD)          | 57.7 (12.12) | 59.7 (11.3)  | 52.7 (12.68)    |          |              |              |          |
| Age group              |       |              |                 |          |              |              |          |
| 18–29                  | 198   | 2.2          | 74              | 37.4     | 124          | 62.6        |          |
| 30–39                  | 463   | 5.2          | 253             | 54.6     | 210          | 45.4        |          |
| 40–49                  | 1226  | 13.7         | 830             | 67.7     | 396          | 32.3        |          |
| 50–59                  | 3176  | 35.6         | 2521            | 79.4     | 655          | 20.6        |          |
| 60–69                  | 2434  | 27.3         | 1909            | 78.4     | 525          | 21.6        |          |
| 70–79                  | 1126  | 12.6         | 951             | 84.5     | 175          | 15.5        |          |
| ≥80                    | 309   | 3.5          | 269             | 87.1     | 40           | 12.9        |          |
| Marital status         |       |              |                 |          |              |              |          |
| Single                 | 957   | 11.6         | 635             | 66.4     | 322          | 33.6        |          |
| Married                | 7310  | 88.4         | 5769            | 78.9     | 1541         | 21.1        |          |
| Gender                 |       |              |                 |          |              |              |          |
| Male                   | 3375  | 37.8         | 2418            | 71.6     | 957          | 28.4        |          |
| Female                 | 5557  | 62.2         | 4539            | 81.7     | 1018         | 18.3        |          |
| Nationality            |       |              |                 |          |              |              |          |
| Saudi                  | 7957  | 89.4         | 6167            | 77.5     | 1790         | 22.5        |          |
| Non-Saudi              | 946   | 10.6         | 768             | 81.2     | 178          | 18.8        |          |
| Chronic kidney disease |       |              |                 |          |              |              |          |
| Yes                    | 146   | 1.6          | 139             | 95.2     | 7            | 4.8         |          |
| No                     | 8786  | 98.4         | 6818            | 77.6     | 1968         | 22.4        |          |
| Cardiovascular conditions |      |              |                 |          |              |              |          |
| Yes                    | 7209  | 80.7         | 6015            | 83.4     | 1194         | 16.6        |          |
| No                     | 1723  | 19.3         | 942             | 54.7     | 781          | 45.3        |          |
| Musculoskeletal conditions |      |              |                 |          |              |              |          |
| Yes                    | 787   | 8.8          | 737             | 93.6     | 50           | 6.4         |          |
| No                     | 8145  | 91.2         | 6220            | 76.4     | 1925         | 23.6        |          |
| Respiratory conditions |       |              |                 |          |              |              |          |
|                        |       |              |                 |          |              |              |          |
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### Table 1

|                      | Total | Polypharmacy | No polypharmacy |
|----------------------|-------|--------------|-----------------|
|                      | N     | %            | N              | %                | N       | %                |
| Yes                  | 961   | 10.8         | 855            | 89.0             | 106     | 11.0             |
| No                   | 7971  | 89.2         | 6102           | 76.6             | 1869    | 23.4             |

### Mental health conditions

|                      | Yes   | 8.6          | 654            | 85.4             | 112     | 14.6             |
| No                   | 8166  | 91.4         | 6303           | 77.2             | 1863    | 22.8             |

### # Chronic conditions

|                      | No coexisting conditions | 1250 | 14.0 | 607 | 48.6 | 643 | 51.4 |
|                      | Single coexisting condition | 2849 | 31.9 | 2018 | 70.8 | 831 | 29.2 |
|                      | >2 coexisting conditions | 4833 | 54.1 | 4332 | 89.6 | 501 | 10.4 |

Asterisks (*) represent significant differences in polypharmacy from X² tests.

*P<0.001, **0.001<P<0.01.

Table 2

| Medication therapy class | Oral antidiabetic agent | Diuretic | Corticosteroid, systemic | Angiotensin II receptor blocker | ACE inhibitor | Non-steroidal anti-inflammatory drugs | PPAR-γ agonist | Anticoagulants | Calcium channel blocker | ACE inhibitor | CCB | Beta-adrenergic blocker, beta-1 | Angiotensin II receptor blocker | Calcium antagonist | Corticosteroids | Anticoagulants | Beta-adrenergic blocker, beta-1 | Angiotensin II receptor blocker | Calcium antagonist | Corticosteroids |
|-------------------------|-------------------------|----------|--------------------------|---------------------------------|--------------|--------------------------------------|----------------|-----------------|------------------------|----------------|------|--------------------------------|---------------------------------|------------------|----------------|-----------------|--------------------------------|---------------------------------|------------------|-----------------|
| Total                   | 7270                    | 81.4     | 407                      | 67                              | 792          | 92                                  | 151            | 92             | 215                   | 232           | 321  | 90                             | 1796                        | 2011             | 215            |
| Antidiabetic agent      | 600                     | 7.9      | 822                      | 9.2                             | 1351         | 15.1                                | 1806           | 2012           | 1894                   | 2321          | 254  | 89                             | 1984                        | 2012             | 1894           |
| Anticoagulants          | 2253                    | 25.2     | 2162                     | 25.2                            | 2253         | 25.2                                | 2253           | 25.2           | 2253                   | 2253          | 25.2 | 25.2                           | 2253                        | 25.2             | 2253           |
| Calcium antagonist      | 6144                    | 72.4     | 2547                     | 30.2                            | 6144         | 72.4                                | 6144           | 72.4           | 6144                   | 6144          | 72.4 | 72.4                           | 6144                        | 72.4             | 6144           |
reduction the healthcare cost.\textsuperscript{38} Pharmacists can help other healthcare providers in detecting polypharmacy, drug interactions and in providing recommendations for simplified medication regimens and minimising medications to positively impact health outcomes of diabetes care.\textsuperscript{39, 40}

We also looked at other related factors for polypharmacy. We observed that women were more likely to have a polypharmacy compared with men, this is consistent with the findings from data among patients with diabetes.\textsuperscript{10} In addition, studies have reported that women in the general population have a higher use of prescribed and non-prescribed medications, and higher healthcare utilisation as compared with men.\textsuperscript{41–44} This could be because women tend to be more concerned about their health and seek health services more often than men.\textsuperscript{45} It has to be noted that the majority of patients with diabetes in our study were women, this is not surprising since the rate of diabetes is higher in women as compared with men in Saudi Arabia.\textsuperscript{2}

**Strengths and limitations**

This study has some limitations; we defined polypharmacy as the cumulative use of five or more medications during a 1-year period rather than the concurrent use of medications, using this definition may have overestimated the rate of polypharmacy. We did not control for the severity of diabetes using the Diabetes Complications Severity Index, which may affect the rate of polypharmacy. We have also only observed filled prescriptions and not actual use of the medications. By using the EHR data, we cannot eliminate some risk of bias; inaccurate information or missing data related to the use of EHR. Due to the cross-sectional nature of the data, it is difficult to assess any causal relationships. People with the end-of-life care were included in the study, which may have also overestimated the rate of polypharmacy.\textsuperscript{16} Moreover, we have included all therapeutic medication classes, including OTC medications and vitamins in our definition, which may have overestimated the rate of polypharmacy. It has to be noticed that not all polypharmacy is harmful; however, we have not assessed if the polypharmacy was appropriate or not. This study was conducted in a tertiary hospital in Riyadh; therefore, the findings from this study cannot be generalised to primary care settings or to other regions in Saudi Arabia. In addition, we cannot exclude selection bias; patients included in this study may be sicker, have sever diabetes and higher rates of comorbidities as compared with individuals seen in primary care settings.

Despite these limitations, this study has many advantages such as the use of large sample size, which allowed us to identify the prevalence of polypharmacy among a subgroup of patients. Furthermore, findings from this study added to the existing literature on the prevalence of polypharmacy among all age groups and identified the individuals who have a high risk of polypharmacy based on their comorbidities. In addition, our results highlighted the need for routine monitoring of high-risk individuals for drug-related problems. Therefore, future studies are required to identify the rate of polypharmacy among other healthcare settings and assess the impact of pharmacist-led interventions on the rate of polypharmacy in patients with diabetes.

**CONCLUSION**

Polypharmacy is very common among adults with diabetes; particularly among individuals with multiple chronic conditions. Older adults patients have a higher rate of polypharmacy, which could be due to the increased number of multiple chronic conditions in this population. Moreover, patients with coexisting cardiovascular, mental and musculoskeletal chronic conditions are at a high risk of polypharmacy. Individuals with diabetes may benefit from simplified treatment regimens; thereby enhancing the health outcomes of this population.
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