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ORIGINAL ARTICLE

Anti-Diabetic Drug Utilization in Fasa, Southern Iran: A Pharmacoepidemiological Study Based on PERSIAN Cohort Data

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ABSTRACT

Background: In order to design better management for anti-diabetic medication, pharmacoepidemiological studies are required to have an update on the drug utilization. Therefore, the present study was performed with the aim of pharmacoepidemiological analysis on utilization of anti-diabetic drugs based on PERSIAN cohort data.

Methods: In this study, 10138 participants were included by baseline data. Use of anti-diabetic medications based on Anatomical Therapeutic Chemical (ATC) code A10 was provided. Quantitative and qualitative variables were illustrated using mean±standard deviation (SD) and frequency (percent). Logistic regression was employed to define associated factors with categorical outcomes.

Results: The descriptive analysis showed that 12.3% (n=1249) of the participants had diabetes, while only 5.3% (n=540) of them had utilized anti-diabetic medications. Totally, 94.7% of the participants did not take any anti-diabetic drug, 3% received monotherapy and 2% reported a combination of anti-diabetic medication therapies. Also, the higher ages showed a more chance for use of anti-diabetic medications (40-59 years: OR=3.72, 95% CI: 2.38-5.81; ≥60, OR=5.61, 95% CI: 3.41-9.22). In addition, married and employed participants were more likely to take anti-diabetic medications. Also, having cardiovascular diseases (CVDs), fatty liver and pregnancy were associated with a higher significant chance of using anti-diabetic medications.

Conclusion: Less than half of the patients diagnosed with diabetes received anti-diabetic drugs indicating the importance of medication adherence training programs in this group of patients.

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Introduction

The prevalence of diabetes has increased substantially in the last 20 years that highlights the need to improve the management of the disease. Numerous factors, including the patient's general health well-being, comorbidities, social environment, psychological

status, and cognitive function can complicate diabetes management. Although, pharmacotherapy for diabetes has recently reached an unprecedented level, the first generation of diabetes drugs (i.e. metformin, sulfonylureas) are still competing with newer groups of medications like glycosidase and glinides inhibitors, thiazolidinedione and incretin-based drugs, and sodium-glucose inhibitors II carriers (1). Different treatment modalities are selected based on patient's blood sugar level, age, body mass index (BMI), genetics background, food intake and activity level (2).

Although the diversity of diabetes medications has increased the available options to manage patients, the related health expenditures in health systems has increased too (3). So, it is crucial to consider specific factors when controlling the blood sugar of patients including the cost of treatment, the side effects, ease of administration, and urgency of blood sugar normalization (4). In addition, it was shown that many diabetic people have difficulty in managing their medication regimens and other aspects of self-control (5). Recently, a pharmacoepidemiological study on diabetes evaluated the actual consequences including risk of cardiovascular diseases (CVDs), mortality, and rare immune complications such as pancreatic cancer or pancreatitis. The level of evidence presented by this type of study depends on use of the most proper techniques, which can limit the risk of bias and misinterpretation (6).

Yousefi *et al.* studied the utilization of anti-diabetic drugs in Iran over a ten-year period (2009-2018). They showed the overall anti-diabetic drug use to be increased by 235.53%, while insulin utilization rose by 148.65% and non-insulin consumption grew by 132.68% (7). Another study performed in Iran between 2000 and 2012 indicated that total drug utilization increased from 4.47 to 33.54 (8). The utilization of drug for treating diabetes showed a rise by 20.1% from 2001 to 2014 and 120% from 2005 to 2014 in Andalusian region (9) and Croatia (10), respectively. Drug utilization experienced a 21% rise between 2012 and 2015 in Poland too. One of the main reasons for this remarkable growth in utilization and not the only one can be the improvement of diagnosis (11).

International Diabetes Federation predicted the prevalence of the global diabetes to reach 10.2% in 2030 and 10.9% in 2045 (12). The Middle East and North Africa regions, where Iran is also located, account the highest prevalence of diabetes worldwide recording 13.3% in 2030 and 13.9 in 2045. Diabetes prevalence in Iran was announced 10.42% in 2022, 67.95% of whom were aware of their condition; while 40.87% were treated for this condition (13). The structure of the Iranian population indicates that over 45% (more than 34 million people) are currently aged over 30 years old, placing them at the risk of developing diabetes (3). In order to design better management for diabetes, more pharmacoepidemiological studies are required to have an update on the drug utilization. Therefore, the present study was performed with the aim of pharmacoepidemiological analysis on utilization of anti-diabetic drugs based on PERSIAN cohort data in the adult population of Fasa city in the south of Iran.

Materials and Methods

Current investigation was a sub-analysis of the Fasa PERSIAN Cohort Study that enrolled 10138 individuals from baseline data of adults in Fasa, southern Iran. The Fasa PERSIAN cohort is a branch of Prospective Epidemiological Research Studies in Iran (PERSIAN). So Fasa PERSIAN Cohort Study is a prospective population-based cohort that evaluates non-communicable diseases (NCDs) in participants aged 35-70 years with a 15-year follow-up (14, 15); while the first data collection was undertaken from 2015 to 2016 and each individual has signed informed consent at the study beginning of the study (14, 15). Including criteria was diagnosis of diabetes (self-report) and completing the needed data. All eligible participants had the same socioeconomic status, with the similar ethnicity and residential region (16). The study protocol was approved by Ethical Committee of Shiraz University of Medical Sciences (code: IR.SUMS.REC.1401.336).

Usage of anti-diabetic medications based on the Anatomical Therapeutic Chemical (ATC) code A10 was provided for each participant and 7 medications were considered for the study consisted of metformin, glibenclamide, gliclazide, acarbose, pioglitazone, repaglinide, and insulin. The main variables used in the analysis were age, gender, marital status, having a job, years of education, having an underlying disease, and being pregnant. In order to characterize quantitative and qualitative variables, mean±standard deviation (SD) and frequency (percent) were used. Logistic regression was employed to assess associated factors with the categorical outcomes. Total data was obtained from analysis by Statistical Package for Social Sciences (SPSS, version 25, Chicago, IL, USA). Differences with a p value< 0.05 were considered statistically significant.

Results

It was shown that 12.3% (n=1249) of the participants suffered from diabetes, while only 5.3% (n=540) used anti-diabetic medications. Almost half of these

participants with diabetes (52.3%) were diagnosed before the age of 50 years and the rest after the age of 50 years. The age of the participants varied from 35 to 92 years, with an average of 48.63±9.57 years. Totally, 54.8% were female and 96.3% were married (88.9%) or divorce-widow (7.4%); while 25.1% and 49.7 had no education and a job, respectively and 33.8% reported no underlying diseases. The results showed that 94.7% of the participants did not take anti-diabetic drugs and among the remaining participants, 3% received monotherapy with anti-diabetic drugs and 2% received a combination therapy. Among 540 out of 10138 participations; 4,3% used metformin that followed respectively by glibenclamide (2.6%), acarbose (0.7%), insulin (0.4%), pioglitazone (0.2%), gliclazide (0.1%), and repaglinide (0.0%).

The Older individuals had more chance of using anti-diabetic medications (40-59 years: OR=3.72, 95%CI: 2.38-5.81; ≥60, OR=5.61, 95%CI: 3.41-9.22). In this regard, married and employed participants were more likely to take anti-diabetic medications; which was probably correlated to an increase in age. On the other hand, having CVDs (OR=3.1, 95%CI: 2.55-3.78) and fatty liver (OR=2.56, 95%CI: 2.06-3.19) were associated with a higher chance of using anti-diabetic drugs. In addition, pregnancy increased the chance of consumption for anti-diabetic medications (p=0.001). Table 1 shows the distribution of participants' characteristics.

Discussion

The results of this large cohort-based study indicated that 12.3 percent of populations were diagnosed with diabetes, while only 5.3 percent of them received medication. On the other hand, almost 50 percent of populations were diagnosed with diabetes before fifty years old; and by increasing age, the probability of intake of anti-diabetic drugs was elevated. It should be mention that some comorbidities such as CVD and fatty liver were significantly correlated with consumption of anti-diabetic medications. Also, being pregnant was remarkably associated with utilization of anti-diabetic drugs. As diabetes is one of the most serious health complications worldwide, especially

Table 1: The distribution of participants' characteristics.

Variable		Antidiabetic drug use		Unadjusted Odds ratio (95%CI)	*P* value	Adjusted Odds ratio (95%CI)	*P* value
		No	Yes				
Age	≤39	2171 (99.0)	23 (1.0)	1	-	Ref	-
	40-59	8976 (94.7)	336 (5.3)	5.31 (3.47-8.12)	<0.001*	3.72 (2.38-5.81)	<0.001*
	≥60	1451 (88.9)	181 (11.1)	11.78 (7.59-18.26)	<0.001*	5.61 (3.41-9.22)	<0.001*
Gender	Male	4428 (96.7)	150 (3.3)	1	-	Ref	-
	Female	5170 (93.0)	390 (7.0)	2.23 (1.83-2.70)	<0.001*	1.19 (0.91-1.55)	0.195
Marital status	Single	370 (98.9)	4 (1.1)	1	-	Ref	-
	Married	8551 (94.8)	466 (5.2)	5.04 (1.87-13.56)	0.001*	3.76 (1.19-11.9)	0.024*
	Divorce-Widow	677 (90.6)	70 (9.4)	9.56 (3.46-26.41)	<0.001*	3.7 (1.14-12.05)	0.030*
Job	No	4653 (92.3)	385 (7.7)	1	-	Ref	-
	Yes	4943 (97.0)	154 (3.0)	2.366 (2.20-3.22)	<0.001*	0.68 (0.53-0.86)	0.002*
Education	Years (Mean±SD)	4.75±3.90	3.01±3.37	0.87 (0.85-0.90)	<0.001*	0.99 (0.95-1.02)	0.375
Cardiovascular diseases	No	753 (97.3)	205 (2.7)	Ref	-	Ref	-
	Yes	2240 (87.0)	335 (13.0)	5.36 (4.48-6.42)	<0.001*	3.1 (2.55-3.78)	<0.001*
Fatty liver	No	8697 (95.7)	388 (4.3)	Ref	-	Ref	-
	Yes	896 (85.5)	152 (14.5)	3.8 (3.11-4.64)	<0.001*	2.56 (2.06-3.19)	<0.001*
Kidney stone	No	7958 (95.0)	417 (5.0)	Ref	-	Ref	-
	Yes	1635 (93.0)	123 (7.0)	1.44 (1.17-1.77)	0.001*	1.14 (0.91-1.42)	0.249
Cancer	No	9539 (94.7)	535 (5.3)	Ref	-	Ref	-
	Yes	54 (91.5)	5 (8.5)	1.65 (0.66-4.14)	0.286	0.90 (0.35-2.37)	0.838
Neurological complications	No	8039 (94.7)	450 (5.3)	Ref	-	Ref	-
	Yes	1554 (94.5)	90 (5.5)	1.04 (0.82-1.31)	0.774	0.85 (0.66-1.09)	0.191
Psychiatric disorders	No	7469 (94.7)	414 (5.3)	Ref	-	Ref	-
	Yes	2124 (94.4)	126 (5.6)	1.07 (0.87-1.31)	0.517	0.90 (0.72-1.12)	0.327
Autoimmune diseases	No	9118 (94.8)	499 (5.2)	Ref	-	Ref	-
	Yes	475 (92.1)	41 (7.9)	1.58 (1.13-2.2)	0.007*	0.93 (0.66-1.33)	0.702
Pregnancy	No	9188 (94.9)	493 (5.1)	Ref	-	Ref	-
	Yes	405 (89.6)	47 (10.4)	2.16 (1.58-2.97)	<0.001*	1.75 (1.24-2.47)	0.001*

*A p value less than 0.05 was considered significant.

in Iran (17), and based on socioeconomic inequality in Iran, insufficient glycemic control in prediabetes and diabetes happens that has enormous burden on the country health system. Therefore, its crucial for patients to be aware of the disease, receiving appropriate treatment, and to have a proper glycemic management (18).

Drug adherence is essential for glycemic control, however only 5.3 percent of our participants received their anti-diabetic medications properly. Our results support the findings from a previous study which suggested individuals with type 2 diabetes to reject the medical care system contact (18). These avoidances are prevalent in the first 5-10 years after diagnosis (19). In order to achieve the effectiveness of the prescribed medications, adherence to therapies is of great importance (20). There are various factors that influence medical adherence in patients with diabetes including economic, social, and cultural status, ageing trend, cognition impairment, regional beliefs, and medical knowledge about the disease and its progression (21). In another study, medication adherence in diabetic patients varied from 4 to 31 percent (22). It should be mention that expenditure of pharmaceutical products per capita in Iran is influenced by various factors especially increase in health costs (23, 24). Despite the fact that oral drugs are usually affordable, while insulin therapy due to insufficient coverage and price is not always available which can be a barrier to treatment (25).

We observed that almost 50 percent of patients were diagnosed with diabetes before fifty years old. As reported before, age, age at diagnosis and duration of diseases cause various complications especially vascular effects in patients with diabetes (26). As Zoungas *et al.* claimed, age, age-onset, and duration of diabetes increased macrovascular events, heart failure and death (27). In contrast, Berkowitz *et al.* revealed that impaired glycemic control is significantly associated with diagnosis of type 2 diabetes at younger age (28). In total, diagnosis at proper time may prevent adverse complications. As we found, older age, being married and employed had a higher association with use of anti-diabetic medications. Since the diabetes pandemic rises, and also people live longer, the diabetes prevalence in the elderly shows an increasing trend (29). Life style factors such as diets with high saturated fatty acids, a low physical activity and changes in carbohydrate metabolism can be correlated to alterations in insulin release and insulin resistance and result in development of diabetes especially in elderly (30). In contrast to our findings, a study by Ramezankhani *et al.* indicated to a relationship between marital status, hypertension and diabetes, which varied by gender; while in males, those never married had a risk factor for hypertension and mortality. However, being widow among women decreased the risk of diabetes (31). Another study revealed that the wives of men with non-communicable diseases such as dyslipidaemia, hypertension, or diabetes were more vulnerable to the complication (32). Although, socioeconomic level has a remarkable effect on the prevalence of diabetes among populations, an inverse association between socioeconomic status and the prevalence of diabetes in the middle-aged people has been demonstrated. This might be due to exposure to some factors that are more common in deprived areas to be a platform for diabetes (33).

We found that those with CVDs, fatty liver and pregnancy had greater chance to receive anti-diabetic drugs. Although anti-diabetics medications and insulin have acceptable availability and coverage in Iran, the control of hyperglycemia, hypertension and hyperlipidemia is not always satisfactory due to high prevalence of chronic vascular diseases among patients with diabetes in Iran (34, 35). Diabetes was shown to be linked to CVDs through putative factors including poor glycemic control, advanced glycation end products, insulin resistance, oxidative stress, and low-grade inflammation (36, 37). Also, fatty liver disease and diabetes are two prevalent conditions that frequently co-exist and up to 70 percent of patients with diabetes might have fatty liver due to occurrence of obesity and insulin resistance; this can subsequently drive adverse complications including macro- and micro- vascular events (38). As obesity and type 2 diabetes have increased specifically over the last 50 years and due to the obesity epidemic and diabetes pandemic, there is a growing number of women with diabetes during pregnancy or gestational diabetes mellitus (GDM) (39). Since the prevalence of GDM has increased worldwide and complications of diabetes among mother and fetus are well known, it is essential to consume anti-diabetic drugs during GDM (40). One of the strengths of our study which enhance its validity is the large sample size of the investigation. Our study has also some potential limitations as we did not have access to blood biomarkers of the patients. Also, due to the fact that the current study examined the population of a specific region, we may not be able to generalize the results to all the people in the society. Thus, it is suggested that more researches to be done in future too.

Conclusion

Less than half of the patients diagnosed with diabetes used anti-diabetic medications, which show the importance of medication adherence training

programs in this group of patients. The age, being married and employed were shown to increase the probability of medication consumption. Also, CVDs, fatty liver and being pregnant increased the chance of using anti-diabetic drugs.

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Authors' Contribution

LZ and RT participated in the conception and design of the study. Both RT and LZ had contributed to the gathering of data. STH performed analysis and interpretation of data. LZ and FD drafted the manuscript. LZ and FD revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Conflict of Interest

None declared.

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