Study on the Side Effects and Complications of Metformin on Diabetic Patients

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ABSTRACT

Metformin is prescribed worldwide, and treatment periods have increased, so, the prevalence of metformin-induced manifestations may have also significantly increased. The main study objective was to assess the self-reported side effects of the prescribed metformin in diabetic patients, to show the metformin complications and to show other uses of Metformin among the study participants. This cross-sectional study was conducted on a selected section of people in the Mecca region in Saudi Arabia from January 2021 to April 2021. Questionnaires were self-administered. The analysis included descriptive analysis in terms of central tendency and dispersion or percentage presentation. Inferential analysis was done using the chi-square test. The sample consisted of 389 respondents from more than five different nationalities. Age and feeling of numbness were statistically related ($p<.01$). There was no substantial link between the age group of the respondent and self-reported indigestion as an effect of metformin, $p=0.205$. The reason for taking metformin was not statistically associated with the self-reported mouth ulcers $p=0.059$. Higher doses, typically lower than 800mg, leads to higher side effects. There were mixed results regarding the duration of medication and the reported side effects, with generally higher incidences of side effects as age increased up to 35 years.

Key Words: *Metformin, Diabetes, Demographics, Side effects, Complications, Uses of Metformin*

eIJPPR 2021; 11(1):28-33

HOW TO CITE THIS ARTICLE: Moussa AM, Sallam AM, Alamri HA, Alghamdi JA, Almohussein NS, Alshahrani SM, et al. Study on the Side Effects and Complications of Metformin on Diabetic Patients. Int J Pharm Phytopharmacol Res. 2021;11(1):28-33. https://doi.org/10.51847/EUdg619

INTRODUCTION

Diabetes Mellitus (DM) is a growing global health concern [1, 2]. The World Health Organization (WHO) has informed that Saudi Arabia ranks the second-highest in the Middle East and is ranked seventh in the world for the percentage of diabetes [3]. It is projected that around 7 million of the population are diabetic, and almost around 3 million have pre-diabetes [4]. Diabetes is a chronic disorder characterized by raised levels of blood glucose, accompanied by troubled metabolism of fats and proteins [5]. Blood glucose upsurges because it cannot be metabolized in the cells due to the deficiency of insulin production by the pancreas or the incapability of the cells to use the insulin that is being produced effectively [1, 6].

The three most prevalent types of diabetes are Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), and Gestational Diabetes Mellitus (GDM) [7]. Insulin deficit, if left unchecked over the long term, can cause damage to many of the body's organs. Consequently, leading to disabling and life-threatening health complications such as cardiovascular diseases (CVD), nerve damage (neuropathy), kidney damage (nephropathy), and eye disease (leading to retinopathy, visual loss, and even blindness). However, if appropriate management of diabetes is achieved, these severe complications can be delayed or prevented altogether [8]. Metformin is one of the most widely used oral hypoglycaemic agents [9]. Although the efficacy and safety of metformin for the treatment of type 2 diabetes

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Received: 10 October 2020; **Revised:** 09 January 2021; **Accepted:** 11 January 2021

mellitus (T2DM) have been well established by its long-term clinical use, the administration of this drug is sometimes associated with adverse events. Gastrointestinal adverse events, including diarrhea, anorexia, and dyspepsia, are common during treatment with metformin but are not severe in most cases. On the other hand, lactic acidosis, which infrequently occurs during metformin treatment, sometimes progresses to a serious condition [10, 11].

However, the side effects and complications of metformin use in Saudi Arabia has not been widely investigated. This study focused on the prevalence of assessing the side effects and complications of Metformin and the factors associated with it in Saudi Arabia patients with type 2 diabetes who were treated with metformin.

Study objectives

The main study objective was to assess the self-reported side effects of the prescribed metformin in diabetic patients, to show the metformin complications and to show other uses of Metformin among the study participants.

MATERIALS AND METHODS

The study was a cross-sectional study conducted on a selected section of people in the Mecca region in Saudi Arabia from January 2020 to April 2020. selected adult population with type diabetes and who are on metformin living in Mecca regions in Saudi Arabia, and agreed to fill the Questionnaire. The total enumeration method was the sampling approach used to recruit population members into the study. Questionnaires were self-administered and required information about demographic variables and metformin drug intake (cause, dose, and duration), any abnormal changes associated with metformin intake in Saudi Arabia. Approval of the study was requested from the Batterjee Medical Collage prior to the implantation of the study. Confidentiality of the information was assured as no personal identifiers were taken. The data were used for research purposes only, and only researchers who were involved in the research had access. All data were preserved in a secure place within IMC premises, both hard and soft copies. Data were collected using an electronic questionnaire (Google Forms) and cleaned for unwanted responses and missing values. The analysis included descriptive analysis in terms of central tendency and dispersion or percentage presentation. Inferential analysis was carried out using the chi-square test at an alpha level of 0.05. The analysis was carried out by the use of SPSS version 25.

RESULTS AND DISCUSSION

The sample consisted of 389 respondents from more than five different nationalities who were residing in Saudi Arabia at the time of the interview. As shown in **Table 1**, the minimum age of the respondents was 20 years, with people aged above 36 consisting of the largest frequency of the age group (41.65%). The highest education level was master's, while 43.2% of the total sample reported having a Bachelor's degree. 72% of the total sample respondents said they used Metformin due to diabetes, while 32.4% said that metformin caused them a low mood of depression. **Figure 1** illustrates the dosage of Metformin used among diabetic patients. **Figure 2** illustrates the frequency distribution for the duration of use.

Table 1. Demographic variables frequencies

Variable	Freq. (%)
Age	
20-25	101(26.0)
26-30	81(20.8)
31-35	45(11.6)
36>	162(41.6)
Education Level	
Bachelor	168(43.2)
Diploma	116(29.8)
Master	45(11.6)
No Education	60(15.4)
Nationality	
Egyptian	22(5.7)
Indian	25(6.4)
Saudi	304(78.1)
Sudanese	16(4.1)
Syrian	17(4.4)
Other	5(1.3)
Knowledge of Metformin	
No	76(19.5)
Yes	313(80.5)
Respondent or Member of the family takes Metformin	
No	110(28.3)
Yes	279(71.7)
Reason for taking Metformin	
Diabetes	280(72.0)
Weight Loss	20(5.1)
Polycystic Ovaries	26(6.7)
Other	63(16.2)
Low Mood or Depression	
No	263(67.6)
Yes	126(32.4)

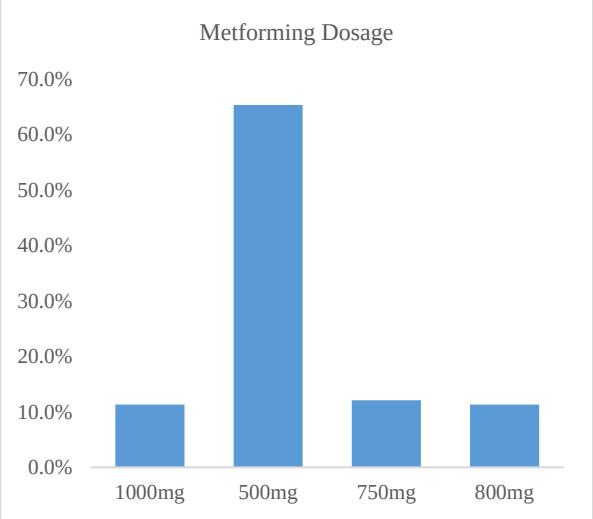

Figure 1. Dosage of Metformin

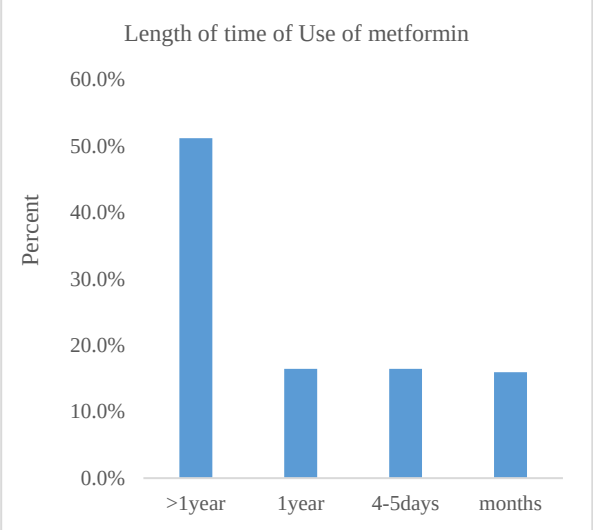

Figure 2. Frequency distribution of the length of time of use

In **Table 2**, age and feeling of numbness were statistically related (p<.01). A higher percentage of the individuals aged between 31 and 35 years said they had feelings of numbness than individuals in the other age groups. Chi-square analysis also showed that Syrians experienced more numbness after using metformin than individuals from other nationalities (58.8%). The least self-reported numbness was experienced by Egyptian nationals in Saudi Arabia at the time of the data collection exercise (31.8%). There was, however, no substantial link between the feeling of numbness and the reason for taking metformin. There was no substantial association between the age group of the respondent and self-reported indigestion as an effect of metformin, p=0.205. However, nationality and self-reported indigestion were significantly associated, where the highest self-reported cases in terms of percentage were Sudanese **(Table 3)**.

Table 2. Chi-square test for association between numbness and demographic variables

Variable	Freq. (%)	p-value
Age		
20-25	31(30.7)	
26-30	24(29.6)	.000
31-35	18(40.0)	
36>	18(11.1)	
Nationality		
Egyptian	7(31.8)	
Indian	9(36.0)	
Saudi	58(19.1)	.001
Sudanese	4(25.0)	
Syrian	10(58.8)	
Other	3(60.0)	
Reason for taking Metformin		
Diabetes	64(22.9)	
Weight Loss	6(30.0)	.167
Polycystic ovaries	10(38.5)	
Other	11(17.5)	
Dosage		
500mg	38(15.0)	
750mg	20(42.6)	.000
800mg	18(40.9)	
1000mg	15(34.1)	
Length of time in Metformin Medication		
4-5 days	17(26.6)	.000
Months	22(35.5)	
1 year	30(46.9)	
1 year >	22(11.1)	

Table 3. Association between self-reported indigestion and demographic variables

Variable	Freq. (%)	p-value
Age		
20-25	52(51.5)	
26-30	39(48.1)	.205
31-35	24(53.3)	
36>	65(40.1)	
Nationality		
Egyptian	17(77.3)	
Indian	11(44.0)	
Saudi	134(44.1)	.025
Sudanese	9(56.3)	
Syrian	9(52.9)	
Other	3(60.0)	
Reason for taking Metformin		
Diabetes	129(46.1)	.951
Weight Loss	10(50.0)	
Polycystic ovaries	13(50)	
Other	28(44.4)	

Dosage		
500mg	110(43.3)	
750mg	24(51.1)	.342
800mg	21(47.7)	
1000mg	25(56.8)	
Length of time in Metformin Medication		
4-5 days	28(43.8)	
Months	32(51.6)	.113
1 year	37(57.8)	
1 year >	83(41.7)	

As shown in **Table 4**, a higher percentage (43.2%) of 26-30-year-old respondents had self-reported having disturbed vision compared to 6.8% of the respondents who had self-reported having disturbed vision. Age group and self-reported vision were statistically associated (p<.01). The more the dosage, the higher the percentage of respondents that said they experienced a disturbed vision. There was also a significant association between dosage and self-reported disturbed vision.

The reason for taking metformin was not statistically associated with the self-reported mouth ulcers (p=0.059). However, the higher the dosage one took, the more likely they were to report mouth ulcers. Nationality was significantly associated with self-reported mouth ulcers (p=.000). However, there were mixed results on how long respondents used metformin with only 15.1% of individuals who used it for more than a year, saying they experienced mouth ulcers and 51.6% of individuals who had used the drug for 1-year reporting mouth ulcers **(Table 5)**.

Table 4. Self-reported disturbed vision

Variable	Freq. (%)	p-value
Age		
20-25	16(15.8)	
26-30	35(43.2)	.000
31-35	16(35.6)	
36>	11(6.8)	
Nationality		
Egyptian	12(54.5)	
Indian	13(52.0)	
Saudi	40(13.2)	.000
Sudanese	5(31.8)	
Syrian	7(41.2)	
Other	1(20.0)	
Reason for taking Metformin		
Diabetes	51(18.2)	
Weight Loss	7(35.0)	.023
Polycystic ovaries	10(38.5)	
Other	10(15.9)	
Dosage		
500mg	22(8.7)	
750mg	13(27.7)	.000
800mg	21(47.7)	
1000mg	22(50.0)	
Length of time in Metformin Medication		
4-5 days	15(23.4)	
Months	21(33.9)	.000
1 year	28(43.8)	
1 year >	14(7.0)	

Table 5. Self-reported Mouth ulcers

Variable	Freq. (%)	p-value
Age		
20-25	35(34.7)	
26-30	35(43.2)	.000
31-35	19(42.2)	
36>	21(13.0)	
Nationality		
Egyptian	9(40.9)	
Indian	16(64.0)	
Saudi	66(21.7)	.000
Sudanese	6(37.5)	
Syrian	10(58.8)	
Other	3(60.0)	
Reason for taking Metformin		
Diabetes	71(25.4)	
Weight Loss	9(45.0)	.059
Polycystic ovaries	12(46.2)	
Other	18(28.6)	
Dosage		
500mg	44(17.3)	
750mg	20(42.6)	.000
800mg	24(54.5)	
1000mg	22(50.0)	
Length of time in Metformin Medication		
4-5 days	19(29.7)	
Months	28(45.2)	.000
1 year	33(51.6)	
1 year >	30(15.1)	

A cross-sectional descriptive design was utilized to provide empirical evidence of self-reported effects of metformin use on respondents of different ages, different nationalities, and the use of metformin for different reasons. The main study objective was to assess the self-reported implications of the use of metformin on diabetic cases, but the study included other uses. By incorporating individuals with different age groups, educational backgrounds, and nationalities, the study aimed at getting as rich primary information as possible hence increasing the validity of the study.

ISSN (Online) 2249-6084 (Print) 2250-1029

With 80.5% of the respondents saying that they had some knowledge of metformin, the views expressed by the respondents could be considered relatively accurate. The study also found that most of the respondents use metformin for diabetes as opposed to just 5.1% of the respondents who said that they use the drug for weight loss and 6.7% for polycystic ovaries. Additionally, 71.7% of the sample respondents reported having one member of the family using metformin, which improves confidence that the respondents have some passive or active experience with the medicine.

Across the different reported effects of metformin, one could observe from the analysis presented in the study that higher dosages were associated with higher instances of self-reported side effects of the drug. This is clear that higher doses of the drug could imply more side effects of the drug regardless of the reason for using the drug. This finding was consistent with that of Cusi & Defronzo, (1998) [12]. It was also observable from the study that non-Saudis experienced side effects of the metformin more than the other nationalities represented in the sample. While there is no evidence yet to explain this finding, one can only conclude that Saudis are less affected by medicine than people from other nationalities [13].

It would be expected that a lengthy use of the medication could either be positively associated with the side effects of metformin medication [14, 15]. However, the present study showed mixed results where, in some of the cases, respondents who had used the medication for longer times experienced higher incidences of the side effects; in other cases, longer use had led to more incidences of the side effects. However, people who used the medication for one year had the highest incidences in almost all the cases investigated in the study. Higher dosages, as expected, attracted more cases of the side effects. A surprising result, however, was that only nationality was significantly associated with self-reported indigestion due to the use of the medication. Higher percentages were also observed across different levels of the demographic variables on self-reported indigestion. This finding suggests that indigestion may significantly increase upon the use of the medication but did so across the different categories with an equal measure so that differences were not significant [16].

The study used primary data to make conclusions about the findings of the data. While the advantage is getting firsthand information from study respondents, there were high chances that respondents may have given dishonest answers, a factor that could not be controlled. The sampling method was the less powerful non-probabilistic sampling (convenience sampling), which may reduce the generalizability of the sample findings to a broader population. Seeing mixed results from the sample, such as inconsistencies in the length of use of the medication and the differences in nationalities, ought to be further investigated in future studies.

In conclusion, the results showed that higher doses, typically lower than 800mg leads to higher side effects. There were mixed results on length of use of the medication and the reported side effects, with generally higher incidences of side effects as age increased up to 35 years.

CONCLUSION

In about one-third of participants, metformin caused them a low mood of depression. Age and feeling of numbness were statistically related, Syrians experienced more numbness after using metformin than individuals from other nationalities. However, nationality and self-reported indigestion were significantly associated. There was also a significant association between dosage and self-reported disturbed vision. Nationality and higher dosage were significantly associated with self-reported mouth ulcers. Therefore, we recommend strict follow up of Metformin users. In addition, we recommend conducting large-scale studies concerning this important topic.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

REFERENCES

[1] Abdulaziz Al Dawish M, Alwin Robert A, Braham R, Abdallah Al Hayek A, Al Saeed A, Ahmed Ahmed R, et al. Diabetes mellitus in Saudi Arabia: a review of the recent literature. Curr Diabetes Rev. 2016;12(4):359-68.

[2] Sindi HA. Evidence that supports the antidiabetic, antihypertensive, and antihyperlipidemic effects of olive (Olea europaea L.) leaves extract and its active constituents (oleuropein) in human. J BiochemTechnol. 2020;11(2).

[3] Ahmed IA, Alosaimi ME, Alkhathami SM, Alkhurayb NT, Alrasheed MS, Alanazi ZM, et al. Knowledge, attitude, and practices towards diabetes mellitus among non-diabetes community members of Riyadh, Kingdom of Saudi Arabia. Int J Pharm Res Allied Sci. 2020;9(1).

[4] Mire-Sluis AR, Das RG, Lernmark A. American diabetes association-http://www. diabetes. org. Diabetes/Metab Res Rev. 1999;15(1):78-9.

[5] Almoraie NM. The role of ıpomoea batatas leaves extract on the treatment of dıabetes ınduced by streptozotocın. Pharmacophore. 2019;10(3).
[6] Allah MA, Abdeen HA, Abdelhady AA, Hosam M, Maghraby MA. Response of inflammatory markers to circuit weight training in Diabetic patients. J Adv Pharm Educ Res. 2019;9(2):37.
[7] Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes Res Clin Pract. 2012;97(3):359-67.
[8] Renda F, Mura P, Finco G, Ferrazin F, Pani L, Landoni G. Metformin-associated lactic acidosis requiring hospitalization. A national 10 year survey and a systematic literature review. Eur Rev Med Pharmacol Sci. 2013;17 Suppl 1:45-9.
[9] Iftikhar R, Qadir A, Iqbal Z, Usman H. Prevalence of vitamin B12 deficiency in patients of type 2 diabetes mellitus on metformin: a case control study from Pakistan. Pan Af Med J. 2014;16(1).
[10] Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, et al. Long-term metformin use and vitamin B12 deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016;101(4):1754-61.
[11] Marar O, Senturk S, Agha A, Thompson C, Smith D. The prevalence of vitamin B12 deficiency in patients with type 2 diabetes mellitus on metformin. Royal Coll Surg Ireland Stud Med J. 2011;4(1):16-20.
[12] Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. Diabetes Rev. 1998;6(2):89-131.
[13] Flory JH, Keating S, Guelce D, Mushlin AI. Overcoming barriers to the use of metformin: patient and provider perspectives. Patient Prefer Adherence. 2019;13:1433.
[14] Chen CB, Eurich DT, Majumdar SR, Johnson JA. Metformin and the risk of prostate cancer across racial/ethnic groups: a population-based cohort study. Prostate Cancer Prostatic Dis. 2017;20(1):122-6.
[15] Diabetes Prevention Program Research Group. Long-term effects of metformin on diabetes prevention: identification of subgroups that benefited most in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. Diabetes Care. 2019;42(4):601-8.
[16] Seelig E, Meyer S, Timper K, Nigro N, Bally M, Pernicova I, et al. Metformin prevents metabolic side effects during systemic glucocorticoid treatment. Eur J Endocrinol. 2017;176(3):349-58.

ISSN (Online) 2249-6084 (Print) 2250-1029