Metformin discontinuation rate among patients with type-2 diabetes mellitus in Basrah, Iraq

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Metformin is a biguanide, first introduced in 1957 as an oral glucose-lowering agent, that reduces plasma glucose by decreasing hepatic glucose output and enhancing insulin-mediated glucose utilization (reduce insulin resistance).[1] The long-term blood glucose-lowering efficacy of metformin is broadly similar to sulfonylureas as monotherapy in patients who are not adequately controlled on nonpharmacological therapy. The sulfonylureas generally cause weight gain, while metformin does not, and may even reduce weight. It reduces plasma glucose by 2-4 mmol/L, corresponding to a decrease in glycated hemoglobin (HbA1C) by 1-2%. Metformin also appeared to be superior to sulfonylureas in cardiovascular protection and patient survival in a UK Prospective Diabetes Study.[2] It is widely accepted as the first line drug, relatively effective, safe, and cheap. It improves hirsutism, normalizes menstrual cycles, and induces ovulation in a substantial number of patients with polycystic ovary syndrome.[1] Furthermore, metformin can be considered as a first-line agent for the prevention of type-2 diabetes.[3] The aim of the present work is to determine, in a cohort of patients with type-2 diabetes mellitus (DM), the discontinuation rate and causes of discontinuation of metformin use.

The study was conducted in a diabetes center in Al-Faiha Hospital, Basrah, Iraq. Patients were followed in the out-patient clinic from 6 months to 4 years. Patients discontinued from using other drugs by doctors for various reasons, such as treatment failure, contraindication, failed follow-up, or follow up of less than 6 months, were excluded from the study. From a total of 2,331 patients with type-2 DM, 1019 (43.7%) used metformin from January 2003 to December 2006. Patients were seen every 1-3 months, and were asked about metformin use in each visit. Metformin therapy was initiated (alone or with other drugs) with a single dose of medication (usually 500 mg) taken with the patient's largest meal to prevent gastrointestinal symptoms. Medication doses may be increased by 500 mg every 1-2 weeks, as indicated by the glycemic control, to a desirable blood glucose level, or the maximum recommended daily metformin dose of 2550 mg according to the recommendation.[1] Patients who are widowed, separated, single, or divorced were considered unmarried. Qualifications (years of school achievement) was divided into 2 groups, 6 years and less, and above. The standing height and weight measurements were completed with the subjects wearing light-weight clothing, and without shoes. Height was measured to the nearest cm, and the weight to the nearest half kilogram (kg). Body mass index (BMI) was calculated as body weight in kg divided by the squared value of body height in meters (kg/m^2). Subjects who smoke at least one cigarette per day during the year before the examination were classified as smokers. The data analysis was performed using Statistical Package for Social Sciences version 8 (SPSS, Chicago, IL, USA).

The total number of patients was 1019 (mean age 51.72±10.8 year), 50.9% male, 86.6% married, 47.1% illiterate, 37.4% obese, 23.3% smoker, and 72.5% urban dwellers. The patient who discontinued metformin totalled 560 (54.9%). Demographic factors associated with discontinuations of metformin (**Table 1**) were male (OR, 0.7; 95% CI, 0.5-0.9; p=0.01), and age ≤50 years (OR, 0.6; 95% CI, 0.4-0.7; p=0.0001). No association between discontinuation and marital status, qualification, BMI, smoking state, or residency were observed. When these variables significantly associated with discontinuation were entered simultaneously into a logistic regression model, only those ages ≤50 years remained significantly associated with discontinuation. The cause of discontinuation was 17.5% due to adverse effects, mainly gastrointestinal, such as diarrhea, colic, and cramps. Patients who stop taking the drugs do not believe in its hypoglycemic effects (66.7%), as no hypoglycemia occurs, or it does not cause marked immediate blood glucose lowering effect. No cause for discontinuation was seen in 15.7% of patients. More than half of our patients in this study stopped metformin against the medical advice. This complicated the management of our patients since using the sulfonylureas alone, or insulin alone, is not effective enough for glycemic control especially with the progress of diabetes.[4] Thiazolidinediones, a carbose as an oral agent, are not available widely in our country due to their high cost. Most of our people self medicate on sulfonylureas, a glibenclamide, which is cheap and available even without prescriptions. More males, aged ≤50 years, discontinued metformin. A similar finding of older age-groups being more adherent to metformin prevention therapy than the young group was found by Walker et al.[5] Adverse effects as a cause of discontinuation of metformin were seen in 17.5%, which is comparable with literature, where up to 20% of patients have gastrointestinal side effects, and 10% cannot tolerate the drug.[1] In practice, maximal doses of the commonly used sulfonylureas will reduce HbA1C

Table 1 - Univariate association of metformin discontinuation with demographic factors.

Variables	Continued n (%)	Discontinued n (%)	OR	95% CI	*p*-value
Gender					
Male	214 (46.6)	305 (54.5)	0.7	0.5-0.9	0.01
Female	245 (53.4)	255 (45.5)			
Age (years)					
≤50	175 (38.1)	279 (49.8)	0.6	0.4-0.7	0.0001
>50	284 (61.9)	281 (50.2)			
Marital status					
Married	388 (84.5)	495 (88.4)	0.7	0.5-1	0.07
Unmarried	71 (15.5)	65 (11.6)			
Qualification (years)					
≤6	225 (49.0)	255 (45.5)	1.1	0.8-1.4	0.2
>6	234 (51.0)	305 (54.5)			
Body mass index					
<30	272 (59.3)	365 (65.2)	0.7	0.6-1	0.05
≥30	187 (40.7)	195 (34.8)			
Smoking					
Yes	101 (22.0)	137 (24.5)	0.8	0.6-1.1	0.3
No	358 (78.0)	423 (75.5)			
Residency					
Urban	334 (72.8)	405 (72.3)	1	0.7-1.3	0.8
Rural	125 (27.2)	155 (27.7)			

OR - odds-ratio, CI - confidence interval

levels by 1.1-1.9%, the same range as metformin and thiazolidinediones.[1] The results show that we are dealing with a misconception of metformin, which is considered the first choice in the management of type 2 diabetes.[1] One of the cause of this misconception is probably the educational level of our subjects, as 47.1% were illiterate, despite 72.5% being from the urban areas.

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