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Original article

Metformin use among obese patients with prediabetes in Qassim, Saudi Arabia: An observational study

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ABSTRACT

Background and aims: The high prevalence of prediabetes and diabetes mellitus and its secondary complications in Saudi Arabia is a major healthcare concern. Evidence suggests that despite evidence-based efficacy and safety, metformin is underutilized in prediabetic obese patients. Thus, the aim of this study was to investigate the use of metformin in prediabetic obese patients in the Qassim region of Saudi Arabia.

Methods: Prediabetic patients' electronic health records were accessed and screened from 2017 to 2021. The inclusion criteria were patients with obesity (BMI $\geq$ 35) diagnosed with prediabetes, and who received metformin. Patients with chronic kidney disease and those using metformin for other diseases were excluded. The first major endpoint of this study was the rate of metformin use among obese, prediabetic individuals. The second major endpoint was the factors associated with metformin prescribing in our cohort. Descriptive statistics were used to report the primary and secondary outcomes. Data are presented as percentages, means, standard deviations (SDs), medians, and interquartile ranges, as appropriate. All analyses were conducted using Stata version 16.1.

Results: A total of 304 prediabetic patients were included in this study after screening the records of 1,789 patients. The average age was found to be 40, and the majority were female (72%). The average BMI was found to be 39.4 kg/m^2, while the average HbA1c was 5.8%. In the entire sample, only 25 (8.22%) obese patients received metformin for diabetes prevention. Among obese patients with a BMI $\geq$ 30, 19 patients (8.7%) received metformin. Metformin users had higher odds of being on statins (OR 2.72, 95% CI 1.01 to 7.36; p = 0.049).

Conclusion: According to the study, metformin is not frequently prescribed to prediabetic obese individuals in the Qassim region of Saudi Arabia. This prevention strategy is a missed opportunity in the management of prediabetes in high-risk patients. Future studies are needed to investigate the root causes of the underuse of metformin and potential interventions to promote evidence-based practice in Saudi Arabia.

1. Introduction

Obesity, is associated with insulin resistance, hyperlipidaemia and hyperglycaemia, which increases the risk of the development of prediabetes and diabetes mellitus (DM) (Esser et al. 2014; Daousi et al. 2006). In Saudi Arabia, obesity accounts for 27% of all non-communicable diseases (NCD) mortality and 15% of all NCD-related disabilities in the country, costing $3.8 billion annually to the economy (Althumiri et al. 2021). There is a high

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prevalence of obesity among diabetic patients in Saudi Arabia (AlShahrani and Care 2021).

Saudi Arabia ranks seventh in the world and second highest in the Middle East for DM (Abdulaziz Al Dawish et al., 2016). It is anticipated that over 7 million Saudis are diabetic and almost 3 million have prediabetes (Alateeq et al. 2020; Abdulaziz Al Abdulaziz Al Dawish et al., 2016). Moreover, it was found that about a quarter of the Saudi population over the age of 30 years is living with prediabetes, which places three million people at risk for developing DM and its secondary complications (AlSaleh et al. 2021; Bahijri et al. 2016). DM is the leading cause of chronic kidney disease and increases the risk for cardiovascular diseases, which are the leading cause of death in Saudi Arabia (Al-Rubeaan et al., 2014; Abdulaziz Al Dawish et al., 2016; metrics, 2019).

Although lifestyle modifications which include maintaining a moderate weight, exercise and a balanced diet are considered as first-line treatment for prediabetes, The American Diabetes Association (ADA) recommends considering the use of metformin for prediabetic with fasting plasma glucose of 100–125 mg/dl or A1C of 5.7–6.4%, especially if they are younger than 60 years old, have a Basal Metabolic Index (BMI) of $\geq$ 35 or have a history of gestational diabetes (Davidson et al., 2021; Patel and Mundi, 2019).

Despite the evidenced base safe and effective use of metformin in prediabetic patients, only a small percentage of prediabetic patients are actually prescribed metformin (Hughes et al. 2022; Moin et al. 2015a). Similarly, studies performed in Saudi Arabia reported very low use of metformin among prediabetic patients (Alfayez et al. 2022). Therefore, the objective of this study was to investigate the prevalence of metformin prescribing among prediabetic obese patients in Saudi Arabia.

2. Methods

2.1. Study design and settings

A retrospective chart review was conducted in two secondary care hospitals in the Qassim region of Saudi Arabia. Data were collected from electronic medical records in the period between January 2017 and December 2021.

2.2. Inclusion criteria, Data collection, and study outcomes

Patients who were obese and had a diagnosis of prediabetes, with a defined HbA1c of 5.7% to 6.4% were included in this study. Patients with polycystic ovary syndrome, heart failure, glomerular filtration rate < 45 ml/min, or those who used other oral hypoglycemic medications were excluded. The patient's information was gathered from hospital's electronic health record systems which include their demographics, BMI, HbA1c, number of metformin uses, including dosage and frequency, number of comorbidities, usage of hypertensive drugs, and statin.

We have two major endpoints in this study. The first major endpoint was the rate of metformin use among obese prediabetic individuals. The second major endpoint was the factors associated with metformin prescribing in our cohort. This study's minor endpoints include describing different metformin dosing regimens when used in prediabetic patients. Another minor endpoint was to show HbA1c and BMI changes among metformin users compared to nonusers.

2.3. Statistical analysis and ethical approval

Descriptive statistics were used to report the primary and secondary outcomes. Continuous variables are presented as means and standard deviations (SD) or medians and interquartile ranges as appropriate. Categorical variables are presented in numbers and percentages. We conducted a univariate analysis using logistic regression to evaluate the association of age, gender, baseline HbA1c, baseline BMI, hypertension, dyslipidemia, antihypertensive medication use, and statin use with the decision to prescribe metformin. The association was assessed using odds ratio (OR), 95 % confidence interval (CI), and p-value < 0.05. All analyses were conducted using Stata version 16.1 (Stata Cor., College Station, TX). The study protocol was approved by the research and ethics committee of the Ministry of Health of Saudi Arabia (H-04-Q-001).

3. Results

A total of 1,789 patient charts were analyzed for this investigation, and 304 patients were included **(**Fig. 1**).** The majority of the participants were female, with a mean age of 40.03 (72.37 %). The sample that was taken was comparable between the two hospitals as shown in Table 1**.** The mean BMI was 39.4 and the mean HbA1c was 5.89%. A total of 52 individuals (17.11%) were identified as having hypertension, and 36 (11.84%) as having dyslipidemia. In terms of medication use, 11.51% of patients took statins to manage their dyslipidemia, while the average number of hypertension drugs taken was 1.73. When separating the sample into two categories based on BMI (30 to < 35 vs $\geq$ 35), more patients, 218 against 86, fall into the morbidly obese category. In the BMI < 35 group, greater percentages of patients had hypertension and dyslipidemia, and used statins. The baseline HbA1c was 5.88% in the BMI < 35 group and 5.89 % in the other group. Among those who received metformin in the study cohort, a greater proportion of patients were observed to have dyslipidemia and were on statins **(**Table 1**).**

The rate of metformin use among obese prediabetic individuals is 8.22% (25 patients). Among the 25 patients who received metformin, 19 had a BMI $\geq$ 35 while 6 had a BMI of < 35 **(**Table 1**).**

None of the factors we analyzed had a statistical association with prescribing metformin, except for statin use. We found that the users of metformin had higher odds of being on statins (OR 2.72, 95% CI 1.01 to 7.36; p = 0.049) (Table 2). The metformin dose was different among the participants, as illustrated in Table 3. Among the BMI $\geq$ 35 group, a total of ten patients received 1000 mg daily, eight patients received 750 mg daily, and one patient received 1,500 mg daily. In the other group, two patients received 750 mg daily, two received 1000 mg daily, and two received 1,500 mg daily. Table 4 summarizes the changes in HbA1c and BMI throughout time. The average HbA1c in individuals who did not take metformin increased from 5.88 % at baseline to 6.17 % by the third reading. On the other hand, in those who received metformin, the HbA1c dropped from 5.95 % to 5.73 %. By the end of the study, metformin users had a mean BMI difference of -1.46 kg/m^2, whereas nonusers had a mean difference of 0.51 kg/m^2.

4. Discussion

The current evidence in clinical practice supports the use of metformin in prediabetic patients to prevent diabetes mellitus, along with a healthier lifestyle (Bansal, 2015; Hostalek et al., 2015). Metformin use is associated with favorable outcomes in the reduction of BMI (basal metabolic index) and improved cholesterol profile (Bansal, 2015; Diabetes Prevention Program Research Group, 2012). The DPP trial in the US has found that metformin is more beneficial to prediabetic patients with higher BMI (Herman and Ratner, 2020; Diabetes Prevention Program Research Group, 2002).

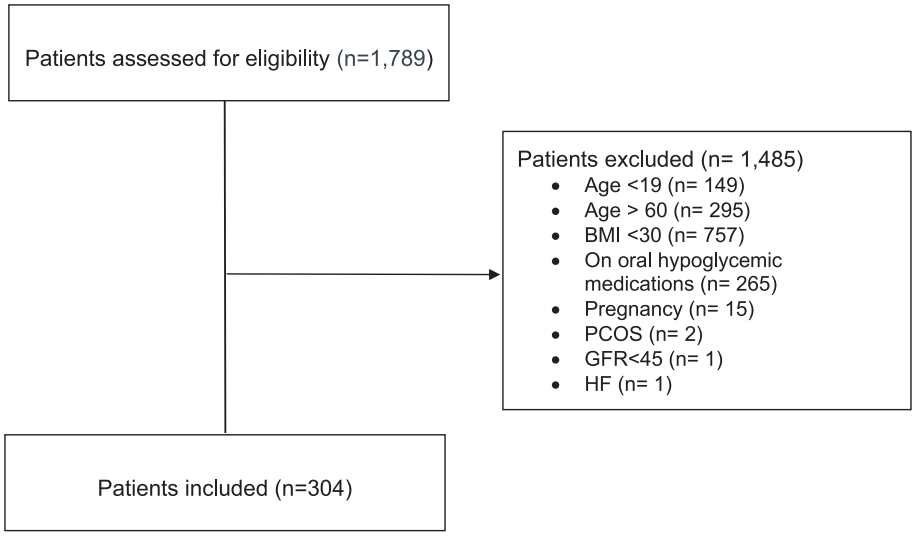

Fig. 1. Study flow diagram.

Table 1
Baseline Characteristics.

		Total (n = 304)	BMI <35 kg/m² (n = 86)	BMI ≥35 kg/m² (n = 218)	Metformin	
					Users	Non-Users
Age, mean (SD)		40.03 (10.92)	42.28 (10.24)	39.14 (11.07)	40.16 (11.61)	40.02 (10.87)
Female, n (%)		220 (72.37)	64 (74.42)	156 (71.56)	15 (60)	205 (73.48)
Hospital, n (%)	BCH	158 (51.97)	39 (45.35)	119 (54.59)		
	KSH	146 (48.03)	47 (54.65)	99 (45.41)		
Hemoglobin A1C, mean (SD)		5.89 (0.21)	5.88 (0.22)	5.89 (0.21)	5.95 (0.21)	5.88 (0.21)
BMI, mean (SD)		39.40 (6.95)	32.11 (1.58)	42.28 (6.10)	39.77 (8.14)	39.37 (6.85)
Comorbidities, mean (SD)		0.70 (0.82)	0.86 (0.83)	0.63 (0.82)	1.0 (1.04)	0.67 (0.80)
Hypertension, n (%)		52 (17.11)	21 (24.42)	31 (14.22)	5 (20)	47 (16.85)
Dyslipidemia, n (%)		36 (11.84)	14 (16.28)	22 (10.09)	6 (24)	30 (10.75)
Metformin use, n (%)		25 (8.22)	6 (6.98)	19 (8.72)	25 (100)	0 (0)
Hypertension Medications, mean (SD)		1.73 (0.66)	1.76 (0.83)	1.71 (0.53)	1.4 (0.55)	1.77 (0.67)
Statin use, n (%)		35 (11.51)	13 (15.12)	22 (10.09)	6 (24)	29 (10.39)
Other Prescription Medications, mean (SD)		1.09 (1.23)	1.21 (1.32)	1.05 (1.19)	1.68 (1.18)	1.04 (1.22)

Data presented as number (%) or mean (SD).
Abbreviations: BMI, body mass index, SD, Standard Deviation, BCH, Buraydah Central Hospital, KSH, King Saud Hospital.

Table 2
Factors associated with metformin prescribing.

Factors	OR	95% CI	P value
Age	1.0	0.96–1.04	0.95
Gender	1.85	0.79–4.29	0.15
Baseline Hemoglobin A1c	3.74	0.68–20.63	0.13
Baseline BMI	1.01	0.95–1.07	0.78
Hypertension	1.23	0.44–3.45	0.69
Dyslipidemia	2.62	0.97–7.07	0.057
Hypertension Medications use	1.23	0.44–3.45	0.69
Statin use	2.72	1.01–7.36	0.049

Table 3
Metformin Dose.

	BMI ≥35 kg/m² (n=19)				BMI <35 kg/m² (n=6)			
Metformin Strength	Metformin Frequency							
	Daily	Twice daily	Three times daily	Total	Daily	Twice daily	Three times daily	Total
500 mg	0	10	1	11	0	2	1	3
750 mg	8	0	0	8	2	1	0	3
Total	8	10	1	19	2	3	1	6

Our study findings showed that only 8% of mainly young, working-age obese and prediabetic patients have been prescribed metformin in Saudi Arabia. This means that only 1 in 12 of these high-risk prediabetic patients receives metformin in Saudi Arabia, despite it is proven through guidelines that the regular use of metformin in prediabetic high-risk patients delays the onset of diabetes and reduces the risk of damage to the long-term complications of diabetes mellitus (Hostalek et al., 2015; Lily and Godwin, 2009; Moin et al., 2015b). Similar results have been observed in the US where only 7.8% of prediabetic and obese patients received metformin therapy (Moin et al. 2015b).

It has been demonstrated from previously published studies that there is a gap of 3–8 years between the onset and diagnosis of diabetes, and 8–16% of patients reported diabetic retinopathy, 17–22% have microalbuminuria and 14–48% developed diabetic

Table 4
Hemoglobin A1C and BMI Changes.

	All patients			Metformin					
				Users			Non-Users		
	All (n = 304)	BMI < 35 kg/m^2 (n = 86)	BMI ≥ 35 kg/m^2 (n = 218)	**All (n = 25)**	BMI < 35 kg/m^2 (n = 6)	BMI ≥ 35 kg/m^2 (n = 19)	**All (n = 279)**	BMI < 35 kg/m^2 (n = 80)	BMI ≥ 35 kg/m^2 (n = 199)
Baseline Hemoglobin A1C, mean (SD)	**5.89 (0.21)**	5.88 (0.22)	5.89 (0.21)	**5.95 (0.21)**	6 (0.24)	5.93 (0.20)	**5.88 (0.21)**	5.88 (0.22)	5.88 (0.21)
Second Hemoglobin A1C, mean (SD)	**6.02 (0.45)**	6.03 (0.34)	6.02 (0.48)	**5.88 (0.39)**	6.3 (-)	5.85 (0.38)	**6.05 (0.46)**	6.02 (0.34)	6.06 (0.50)
Third Hemoglobin A1C, mean (SD)	**6.11 (0.48)**	6.24 (0.44)	6.05 (0.49)	**5.73 (0.57)**	- (-)	5.73 (0.57)	**6.17 (0.44)**	6.24 (0.44)	6.13 (0.46)
Baseline BMI, mean (SD)	**39.40 (7.0)**	32.11 (1.58)	42.28 (6.09)	**39.77 (8.14)**	30.35 (0.51)	42.75 (7.02)	**39.37 (6.86)**	32.24 (1.55)	42.23 (6.02)
Last BMI, mean (SD)	**39.73 (7.34)**	32.34 (4.59)	41.24 (6.87)	**38.31 (6.05)**	27 (-)	39.12 (5.37)	**39.88 (7.47)**	32.56 (4.55)	41.50 (7.01)

peripheral polyneuropathy at the time of diagnosis (Herman and Ratner, 2020; Rhee et al., 2010). There is a lack of data reported in Saudi Arabia which established the number of prediabetic patients reporting microvasculature and microvasculature complications at the time of the diagnosis of diabetes. However, in Saudi Arabia, 28% of diabetic patients develop mild to severe diabetic retinopathy, 20% reports diabetic neuropathy, 1.2% reports microalbuminuria, 1.8% have macroalbuminuria and 1.5% of the patient developed end-stage renal disease (Al-Rubeaan et al. 2014; Alwin Robert, Al Dawish, and Research 2019; Wang et al. 2014). These statistics reflect the gravity of diabetic complications in Saudi Arabia and highlighted the need for a pre-emptive approach, which could be the initiation of metformin in high-risk prediabetic patients.

Healthcare providers' timely intervention in initiating metformin therapy is critically important in high-risk patients with prediabetes (Moin et al. 2015b; Hughes et al. 2022). However, healthcare providers in Saudi Arabia are reluctant to prescribe metformin to high-risk pre-diabetic patients, which showed their lack of awareness and knowledge of evidence-based recommendations (Alfayez et al. 2022). The findings of this study confirm this, as the majority of obese prediabetic patients were not prescribed metformin by healthcare providers.

The healthcare transformation plan of Vision 2030 of Saudi Arabia envisages improving healthcare indicators in the country with a special focus on the prevention of chronic diseases through effective management and monitoring (Rasheed et al., 2020; Chowdhury et al., 2021). Therefore, a lack of translation of a guideline established, safe and effective therapy of metformin in prediabetic patients in Saudi Arabia, is problematic and needs to be addressed.

The reason for the low prevalence of metformin prescription in prediabetic high-risk patients is not clear, therefore future studies should evaluate physician-patient and organizational-level issues that could contribute to the underuse of metformin.

5. Conclusion

In conclusion, the findings of this study indicate that metformin is rarely prescribed to obese prediabetic patients for the prevention of diabetes in the Qassim region of Saudi Arabia. This prevention strategy is a missed opportunity in the pre-diabetes management of high-risk patients. Future studies are needed to investigate the root causes of the underuse of metformin and potential interventions to promote evidence-based practice in Saudi Arabia.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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