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Metformin and Diabetes Prevention in Patients with Prediabetes: Results from Isfahan Diabetes Prevention Study (IDPS)

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AA and MA, contributed to IDPS concepts, design, and revising the manuscript. Author PKS contributed to concepts and design of this sub-study, and data collection, drafting, writing of the manuscript. Author AF contributed to statistical analysis, data interpretation, manuscript drafting, and revising. Author MF contributed to the IDPS concepts, design, and data collection. Authors AA and MA supervised the current study. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Although, the effectiveness of metformin in diabetes treatment is well established, its preventive effect in the development of diabetes is still unclear in real world. We aimed to determine the effectiveness of metformin therapy as a single preventive agent in patients with prediabetes in a cohort study (IDPS).
Study Design: In this prospective observational study.
Place and Duration of Study: Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
Methodology: We included 410 patients with prediabetes (168 metformin user, 242 non-users), who participated in IDPS. To determine the association between metformin use and incidence of

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type 2 diabetes, Cox proportional hazard method, Kaplan-Meier and log Rank test were used.
Results: In fully adjusted model for all confounders, significant hazard ratio (HR) for staying prediabetes rather than returning to normal was detected in male group of metformin non-user (HR: 2·41 [95% CI 1.01-5.79]; P<0·05) and those metformin non-user who had both Impaired Fasting Glucose and Impaired Glucose Tolerance (IFG & IGT) (HR: 2.13 [95% CI 1.05-4.34]; P=0·04). There was no significant difference in terms of developing diabetes risk between metformin users and non-users.
Conclusion: This study evidenced that males and patients with IFG & IGT who had not used metformin are at higher risk to staying prediabetes than returning to normal.

Keywords: Diabetes; prediabetes; IFG; IGT; metformin.

ABBREVIATIONS

T2DM : Type 2 diabetes mellitus
BMI : Body mass index
WC : Waist circumference
HC : Hip circumference
WHR : Waist to hip ratio
LDL : Low-density lipoprotein
HDL : High-density lipoprotein
TC : Total cholesterol
FPG : Fasting plasma glucose
OGTT : Oral glucose tolerance test
IFG : Impaired fasting glucose
IGT : Impaired glucose tolerance
NGT : Normal glucose tolerance
SD : Standard deviation
ANOVA : Analysis of variance.

1. INTRODUCTION

The global prevalence of diabetes was 451 million (age 18–99 years) in 2017 which is estimated to rise to 693 million by 2045. Moreover, it was estimated that there were 374 million people with impaired glucose tolerance (IGT), globally [1]. Iran is one of the 19 countries of the IDF-MENA region (International Diabetes Federation- Middle East and North Africa) and has the third rank in the prevalence of diabetes among them [2]. National Program for Prevention and Control of Diabetes (NPPCD-2016) reported the proportions of type 1 diabetes, types 2 diabetes, and other types of diabetes were respectively 11.4%, 85.5%, and 1.3% in Iran [3]. Diabetes is responsible for many complications, which can reduce quality of life and life span, and impose financial burden to the family and national health care system [4,5]. Therefore, diabetes prevention policies are the governments' interests.

Metformin is known as an insulin sensitizer agent and its efficacy in diabetes treatment is well established [6]. The diabetes studies in the US [7], the UK [8], China [9, 10], and India [11] have revealed that lifestyle modification (LSM) by changing diet and physical activity, and pharmacological agents such as metformin [7]), troglitazone [12,13] and acarbose [14], delayed or prevented the progression of IGT to diabetes.

Although, American Diabetes Association (ADA) has recommended metformin for diabetes prevention in its "Standards for Medical Care in Diabetes" guidelines since 2007, it is not approved by the US Food and Drug Administration (FDA) for prediabetes [15]. Moreover, in studies that evaluated the effectiveness of LSM and metformin, LSM was more effective in reducing the incidence of diabetes compared to metformin. Despite the several studies on the efficacy of metformin in prevention of diabetes, it seems that there has been an active argument for the validation and benefit of using metformin to delay or prevent diabetes progression in real world. Therefore, in this prospective observational study, the effectiveness of metformin treatment as a single preventive agent for diabetes in a cohort of patients with prediabetes has been investigated.

2. METHODS AND MATERIALS

2.1 Study Design and Participants

Subjects in the present prospective observational study are the first-degree relatives (FDRs) of patients with type 2 diabetes who participated in IDPS, an ongoing cohort study in central of Iran, which recruited between 2003 and 2005 and followed up until 2019. In current secondary study, those people who were diagnosed as having pre-diabetes with 75-gram OGTT (oral glucose test tolerance) at baseline have been tested, annually, and individuals with normal OGTT (NGT) have been tested at 3-year intervals [16]. Metformin has been recommended by our physicians to all of participants with prediabetes. Metformin was initially administered

with 500 mg/d dosage and then the dose was increasing to 1500 mg daily according to patient tolerance and fasting plasma glucose aim to less than 100 mg/dl. However, it has been taken by only 168 participants that were defined as metformin users. The rest of them were 242 patients with prediabetes and sub-grouped as metformin non-users. The mean follow-up time for these patients was 5 years. Information including demographic, anthropometric measures, biochemical (fasting plasma glucose, low-density lipoprotein, high-density lipoprotein, cholesterol, triglycerides, glycosylated hemoglobin) and clinical data (blood pressure) were obtained from the registry of Isfahan Endocrine and Metabolism Research Center.

2.2 Anthropometric Assessment

Anthropometric indices [weight, height, waist circumference (WC) and hip circumference (HC)] were measured by well-trained examiners at baseline while participants were minimally clothed and without footwear [17]. Body mass index (BMI) was calculated as weight in kilogram divided by square of height in meter.

2.3 Laboratory Measurement

A blood sample was drawn from all participants after 10 h overnight fasting. Biochemical tests including glycosylated hemoglobin (HbA1c), total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were performed for all samples in addition to oral glucose tolerance test. For OGTT, plasma glucose was measured using venous blood sample at 0, 30, 60, and 120 min after oral glucose administration [17]. If FPG was between 100 mg/dL to 125 mg/dl, and 2-hour post 75 g glucose load was less than 140 mg/dl, the diagnosis was impaired fasting glucose (IFG). If 2-h post glucose load was between 140 mg/dL to 199 mg/dL with normal fasting glucose (FPG<100 mg/dl), the diagnosis was impaired glucose tolerance (IGT). Pre-diabetes were defined as category to encompass either IFG or IGT or both (IFG&IGT) [18,19]. If FPG ≥126 mg/dl and/ or 2-h post glucose load was ≥ 200 mg/dl, the diagnosis of diabetes was done. FPG<100 mg/dl and 2-h post glucose load < 140 mg/dl were considered as normal glucose tolerance (NGT) [19].

All above mentioned biochemical tests were assessed using standardized procedures in the central laboratory of the Isfahan Endocrine and Metabolism Research Center [20].

2.4 Assessment of Blood Pressure

Blood pressure was measured using a mercury sphygmomanometer while subjects were in seated position two times with at least 30s interval between measurements and the mean was recorded as the subject's blood pressure. According to the JNC and WHO Guideline criteria, hypertension was defined as systolic blood pressure ≥ 130 mmHg, Diastolic blood pressure ≥ 85 mmHg and/or taking anti-hypertensive medications [21].

2.5 Other variables Assessment

Demographic information including age, gender, educational level [illiterate, under-diploma, diploma (a formal 12-year education), and university graduate], smoking status and physical activity (Min/week) was collected by survey questions.

2.6 Statistical Analysis

Statistical analyses were performed by SPSS (version 16, SPSS, Inc., IL, United States). P-value< 0.05 was considered statistically significant. Continuous quantitative and categorical data were presented as mean ± standard deviations (SD) and number (percentage), respectively. Normality of quantitative data was evaluated using Kolmogorov-Smirnov test and Q-Q plot.

Independent samples t-test and Chi-squared test were used for comparing quantitative and qualitative variables, respectively, in user and non-metformin user. Comparisons of quantitative and qualitative variables between different final status (normal, prediabetes, diabetes) were conducted using analysis of variance (ANOVA) and Chi-squared tests.

Cox proportional hazard method, Kaplan-Meier and log Rank test were used to determine the association between metformin use and incidence of type 2 diabetes. We adjusted our models for all confounders.

3. RESULTS AND DISCUSSION

In this study, among all participants with prediabetes, 19.3% (n=79) had developed diabetes and 27% (n=112), had become normal during mean 5 years follow-up time (range: 1-11 years). Metformin users were 40% (n=168) and the median usage time was 2 years (range 1-7 years).

The baseline demographic and anthropometric and biochemical characteristics of study participants in Metformin user and non-use at the beginning of study have been shown Table 1. Table 2 shows average of glucose-related data at during follow up period. In our study, metformin non-users were male (p<0•001) and non-educated participants (p=0•026), and those who had IFG (p=0•012) and lower BMI (p<0•001) and lower hip circumference (p<0•001), and higher plasma glucose after 60 (p=0•011), 120 min (p=0•031) and cholesterol (p=0.006) at baseline. The mean BMI (p=0•002), hip circumference (p<0•001), waist (p=0.045) and plasma glucose 120 (p<0•001) were significantly higher in metformin users.

We compared all basic demographic, anthropometric measures and clinical characteristics of study participants at baseline (Table 3) and at end of follow up period (Table 4) between three categories of final glucose tolerance status of participants at the end of follow up i.e. NGT, prediabetes, and diabetes.

Kaplan Meier survival analysis and Log rank test (P>0.1) showed no significant difference in terms of risk of developing diabetes or staying prediabetes between metformin users and non-users (Fig. 1).

The results of crude and adjusted Cox's proportional hazard models are shown in Table 5. Significant hazard ratio (HR) for staying

Table 1. Basic demographic and clinical characteristics of study participants in user and non-Metformin user at the beginning of follow up[1]

Characteristic		Start of study		
		Metformin non-user (N=242)	Metformin user (N=168)	P-value
Gender	Male	86 (35.5%)	156 (64.5%)	<.0.001*
	Female	23 (13.7%)	145 (86.3%)	
Status-base	IFG	152 (62.8%)	83 (49.4%)	0.012*
	IGT	34 (14.0%)	40 (23.8%)	
	Both	56 (23%)	45 (26.8%)	
Education	Illiterate	5 (21%)	5 (3.1)	0.026*
	Under-diploma	103 (43.8%)	94 (58.4%)	
	Diploma	86 (36.6%)	42 (26.1%)	
	University graduate	41 (17.4%)	20 (12.4%)	
Smoking	No-smoker	148 (61.2%)	106 (63.1%)	0.691
	Smoker	94 (38.8%)	62 (36.9%)	
Age (year)		42.62 ± 6.25	44.45 ± 6.16	0.004*
BMI (kg/m^2)		27.83 ± 3.55	29.81 ± 3.87	<0.001*
Weight (kg)		72.96 ± 11.55	74.04 ± 5	0.342
Waist (cm)		88.30 ± 9.29	89.95 ± 9.09	0.075
Hip circumference (cm)		105.58 ± 7.36	108.94 ± 8.15	<0.001*
WHR		0.83 ± 0.06	0.82 ± 0.07	0.172
Fasting plasma glucose (mg/dL)		95.64 ± 11.15	97.44 ± 10.50	0.102
plasma glucose 30 min (mg/dL)		146.09 ± 30.02	146.48 ± 25.50	0.896
plasma glucose 60 min (mg/dL)		146.36 ± 37.13	155.88 ± 34.63	0.011*
plasma glucose 120 min (mg/dL)		117.45 ± 31.35	124.36 ± 31.90	0.031*
Triglyceride (mg/dL)		155.28 ± 95.11	175.23 ± 110.70	0.055
Cholesterol (mg/dL)		191.59 ± 37.21	202.61 ± 42.61	0.006*
HDL (mg/dL)		44.35 ± 11.24	44.89 ± 11.19	0.636
Physical activity (Min/week)		36.04 ± 57.15	41.52 ± 86.54	0.440
HbA1c (%)		5.15 ± .73	5.11 ± .71	0.631
Systolic BP (mmHg)		110.60 ± 10.53	110.74 ± 10.48	0.353
Diastolic BP (mmHg)		70.55 ± 10.15	70.70 ± 10.03	0.187

[1]*Values are Mean ± SD and number (percentage); BP, blood pressure; WHR, waist to hip ratio*

Table 2. Average of glucose-related data at during follow up period[1]

	During follow up time		
	Metformin non-user (N=242)	**Metformin user (N=168)**	**P-value**
Fasting plasma glucose (mg/dL)	101.91 ± 11.10	101.83 ± 8.01	0.930
plasma glucose 30 min (mg/dL)	155.58 ± 22.36	159.62 ± 26.41	0.100
plasma glucose 60 min (mg/dL)	166.51 ± 33.33	171.26 ± 31.48	0.152
plasma glucose 120 min (mg/dL)	128.33 ± 26.39	137.11 ± 27.25	<.0.001*
HbA1c (%)	5.43 ± 0.44	5.51 ± 0.43	0.080

[1] *Values are Mean ± SD*

Table 3. Baseline variables comparison in different final glucose tolerance status [1]

		Normal	**Prediabetes**	**Diabetes**	**P-value**
n		112	219	79	
Follow-up (yr)		5.33 ± 2.62	5.36 ± 3.06	4.98 ±2.981	0.609
Gender	Male	31 (27.7%)	56 (25.6%)	22 (27.8%)	0.883
	Female	81 (72.3%)	163 (74.4%)	57 (72.2%)	
Status-base	IFG	80 (71.4%)	121 (55.3%)	34 (43.0%)	0.002*
	IGT	16 (14.3%)	41 (18.7%)	17 (21.5%)	
	Both	16 (14.3%)	57 (26.0%)	28 (35.4%)	
Metformin	Non-user	75 (67.0%)	126 (57.5%)	41 (51.9%)	0.092
	User	37 (33.0%)	93 (42.5%)	38 (48.1%)	
Smoking	No-smoker	80 (71.4%)	143 (65.3%)	31 (39.2%)	<0.001*
	Smoker	32 (28.6%)	76 (34.7%)	48 (60.8%)	
Education	Illiterate	1 (0.9%)	8 (3.8%)	1 (1.3%)	0.058
	Under-dip	55 (51.4%)	16 (50.2%)	36 (46.2%)	
	Diploma	34 (31.8%)	59 (28.0%)	35 (44.9%)	
	university graduate	17 (15.9%)	38 (18.0%)	6 (7.7%)	
BMI (kg/m^2)		28.62 ± 4.01	28.61 ± 3.58	28.77 ± 4.15	0.948
Age (years)		41.88± 5.72	43.79 ± 6.33	44.29 ± 6.53	0.012*
Physical activity (Min/week)		31.26 ±57.36	41.10 ±80.41	40.43 ±57.53	0.467
Weight (kg)		73.50 ± 11.66	73.34 ±10.80	73.44 ±12.29	0.992
Waist (cm)		87.96 ± 9.30	89.20 ± 9.00	89.83 ± 9.77	0.341
Hip circumference(cm)		107.08 ± 7.75	106.85 ±7.59	107.13 ±8.79	0.949
WHR		0.82 ± 0.06	0.83 ± 0.07	0.83 ± 0.06	0.143
Fasting plasma glucose (mg/dL)		93.69 ± 10.19	96.90 ±10.34	98.73 ±12.70	0.004*
plasma glucose 30min (mg/dL)		138.45±26.12	148.17±27.56	151.89±31.02	0.002*
plasma glucose 60min (mg/dL)		134.31±34.95	151.11±34.15	169.74±34.46	<0.001*
plasma glucose 120min (mg/dL)		106.75±28.21	123.11±31.06	131.65±32.05	<0.001*
Triglyceride (mg/dL)		158.30±122.30	155.55±82.03	191.65±114.29	0.023
Cholesterol (mg/dL)		193.91±49.91	197.30±35.56	195.69±34.33	0.764
HDL (mg/dL)		44.59 ± 11.21	45.44 ±11.64	42.22 ± 9.75	0.102
HbA1c (%)		5.05 ± 0.64	5.16±0.74	5.19 ± 0.76	0.378
Systolic BP (mmHg)		110.43± 10.58	110.78±10.56	110.64±10.20	0.157
Diastolic BP (mmHg)		70.53± 10.16	70.64± 10.11	70.67 ± 10.01	0.628

[1] *Values are Mean ± SD and number (percentage); BP, blood pressure; WHR, waist to hip ratio; Dip, Diploma*

prediabetes was detected in metformin non-users compared to non-user in male (HR: 2•41 [95% CI 1.01-5.79]; P<0•05) and those who had both Impaired Fasting Glucose and is Impaired Glucose Tolerance (IFG & IGT) (HR: 2.13 [95% CI 1.05-4.34]; P=0·04) in fully adjusted model for all confounders. No signification association was found between metformin use and being diabetic or normal glucose tolerance at the end of follow up in our study.

According to our results, it seems that in IFG & IGT, the HR of staying prediabetes for those who did not use metformin were 2.13 times higher than for those who used metformin (P= 0.04, 95% CI: 1.05-4.34). Insulin resistance, and chronic inflammation is a usual observation in context of prediabetes, however, these subjects are worse in IFG & IGT population [22]. Qingguo Lu et al, had investigated the alterations of insulin resistance, chronic inflammation in the IFG, IGT and IFG&IGT groups. They had found an increasing trend for IL-6 and decreasing trend for adiponectin in normal glucose tolerance, IFG, IGT, IFG*IGT groups [22]. In view of these results, it seems that IFG&IGT group might have more serious problem in insulin resistance and chronic inflammation than IFG or IGT groups. Hence, metformin treatment could be more helpful in this subgroup.

The Chinese Diabetes Prevention Program and Early Diabetes Intervention Trial in the UK also showed the beneficial changes in reducing the risk of diabetes with metformin therapy [8,9]. They also observed that metformin was more effective in subjects with IFG for diabetes prevention and acarbose therapy was more helpful in patients with IGT. These observations support the idea that the effectiveness of metformin therapy could be different in subject with IFG, IGT or both.

The Diabetes Prevention Program (DPP) and its follow-up over 15 years, the Diabetes Prevention Program Outcomes Study (DPPOS) evidenced that metformin reduces the development of diabetes. The most benefitted subsets are those subjects with higher baseline fasting glucose or HbA1c and women with a history of GDM [23].

Madsen et al. [24] have reviewed fifteen studies, which compared metformin and life style modification in patient with prediabetes for diabetes prevention. It was concluded metformin compared to intensive diet and exercise does not provide an additional benefit in reducing the onset of diabetes [24]. According to the DPP, effectiveness of metformin was about half in comparison with diet and exercise in delaying the incidence of diabetes overall. But it was approximately ineffective in older individuals (60 years of age) or in those who were less overweight (BMI 30 kg/m2). On the other hand, metformin and life-style modification were equally effective in younger aged individuals and in those who were overweight [7]. In order to these results ADA recommend metformin therapy for prevention of type 2 diabetes especially for those with BMI ≥35 kg/m2, those aged <60 years, and women with prior gestational diabetes mellitus [25].

Authors evidenced that in patients with prediabetes the metformin therapy reduces the level of pericoronary fat inflammation and coronary endothelial dysfunction and may reduce the risk of major adverse cardiac events through adiponectin mimicking effect [26,27].

Table 4. Mean values of anthropometric and clinical characteristics of study participants at the end of follow up period in different final glucose tolerance status [a]

	Normal	Prediabetes	Diabetes	P-value
n	112	219	79	
Follow-up (yr)	5.33 ± 2.62	5.36 ± 3.06	4.98 ± 2.98	0.609
BMI (kg/m2)	29.61 ± 4.11	29.60 ± 4.01	29.62 ± 4.40	0.636
weight (kg)	75.84 ± 12.16	74.86 ± 11.42	74.71 ± 12.34	0.734
waist (cm)	93.27 ± 9.53	93.94 ± 8.80	93.74 ± 9.24	0.816
Hip circumference (cm)	106.35 ± 7.21	105.84 ± 7.68	105.88 ± 8.55	0.843
WHR	0.87 ± 0.06	0.88 ± 0.058	0.88 ± 0.06	0.293
Fasting plasma glucose (mg/dL)	97.29 ± 6.26	101.74± 6.94	108.78 ± 15.86	<0.001*
plasma glucose 30min (mg/dL)	148.90 ± 19.36	157.84 ± 22.83	167.20 ± 29.28	<0.001*
plasma glucose 60min (mg/dL)	152.80 ± 29.47	168.53 ± 27.14	190.43 ± 38.02	<0.001*
plasma glucose 120min (mg/dL)	114.57 ± 20.38	132.64 ± 22.55	154.52 ± 29.54	<0.001*
Triglyceride (mg/dL)	150.73 ± 87.67	154.67 ± 64.67	168.55 ± 60.03	0.207
cholesterol (mg/dL)	197.87 ± 28.30	199.03 ± 29.74	198.29 ± 26.00	0.937
HDL (mg/dL)	45.91 ± 8.87	45.57 ± 9.41	43.58 ± 8.24	0.171
LDL (mg/dL)	102.81 ± 20.79	106.40 ± 25.80	110.00 ± 46.08	0.400
HbA1c (%)	5.38 ± .38	5.46 ± .41	5.59 ± .57	0.005*
Systolic BP (mmHg)	110.36 ± 10.25	110.65 ± 10.21	110.66 ± 10.36	0.114
Diastolic BP (mmHg)	70.58 ± 7.70	70.66 ± 8.00	70.62 ± 7.40	0.697

[1] *Values are Mean ± SD and number (percentage); BP, blood pressure; WHR, waist to hip ratio*

Table 5. Hazard risk ratio and 95% confidence interval of the association between metformin usage and diabetes or prediabetes status in future

	Total	Gender		Initial glucose tolerance status		
		Male	Female	IFG	IGT	IFG&IGT
Staying prediabetes as final glucose tolerance status						
Crude	1.08 (0.83-1.41)	1.24 (0.65-2.36)	1.08 (0.79-1.47)	0.90 (0.62-1.32)	1.38 (0.73-2.58)	1.25 (0.73-2.13)
Model 1	1.06 (0.81-1.38)	1.13 (0.58-2.18)	1.07 (0.79-1.46)	-	-	-
Model 2	1.16 (0.85-1.59)	2.41 (1.01-5.79)*	1.00 (0.69-1.45)	0.93 (0.60-1.43)	1.12 (0.44-2.85)	2.13 (1.05-4.34)*
Developing diabetes as final glucose tolerance status						
Crude	1.18 (0.76-1.85)	1.57 (0.61-4.09)	1.09 (0.64-1.86)	1.37 (0.69-2.70)	1.17 (0.43-3.19)	1.30 (0.59-2.85)
Model 1	1.26 (0.80-1.98)	2.02 (0.73-5.56)	1.19 (0.69-2.05)	-	-	-
Model 2	1.22 (0.72-2.07)	0.07 (0.00-1.51)	1.05 (0.56-1.97)	0.84 (0.30-2.31)	1.75 (0.29-10.62)	2.09 (0.68-6.41)

Crude model: without any adjustment. Model 1: adjustment was made for gender. Model 2: additional adjustment was made for age, education, smoking, other drug consumption, blood sugar, Systolic blood pressure, TG, HDL at baseline, and mean fasting plasma glucose, HbA1c, HD

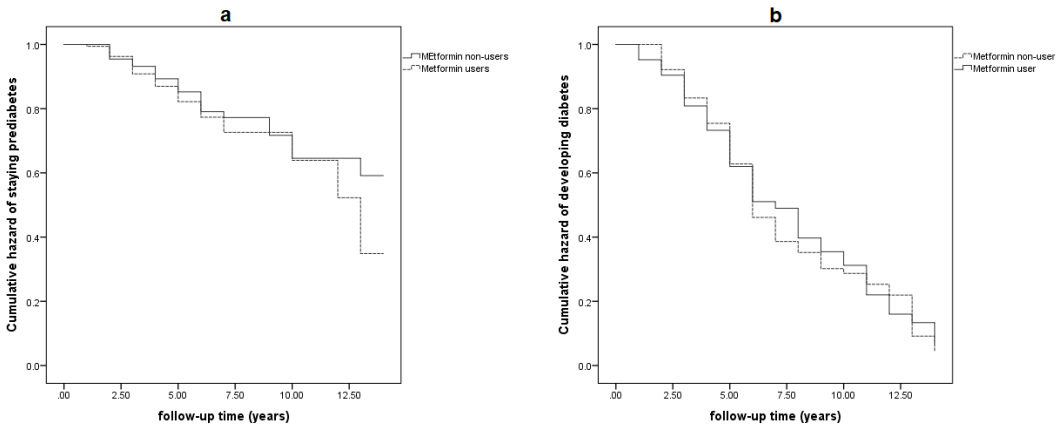

Fig. 1. Kaplan-Meier curves for metformin users and non-users according to final glucose tolerance status (P>0.1): a) staying prediabetes b) developing diabetes

In this regard, we suggest metformin therapy for all patients with prediabetes to get benefit from cardiovascular protection although our study did not show its preventive effect on diabetes development.

Recently a new argument was opened against metformin therapy for diabetes prevention. It is possible that antihyperglycemic treatment drugs do not delay or prevent the development of diabetes. These drugs have only keep a level of glycaemia lower than the diagnostic criteria for diabetes. After stopping these drugs, the prevalence of diabetes in treated individuals and control group are almost equal. In other word these drugs only mask the problem [28].

A few limitations should be taken into consideration when interpreting our findings. We considered lifestyle just at baseline and we did not have access to the data of participant's lifestyle during follow-up period. On the other hand, it was an observational and real world study. Therefore, it was not possible to control the dosage and duration of metformin use in our patients. We suggest future studies in clinical trial settings. The strength of our study is long term follow-up time and evaluating the benefit of using metformin to reduce diabetes risk in different subtype of prediabetes.

4. CONCLUSION

This study provides evidence regarding those patients with IFG&IGT who had not used metformin were at higher risk to staying prediabetes than getting normal. Therefore, the effectiveness of metformin therapy could be different in subject with IFG, IGT or both. Metformin has not prevented diabetes in patients with prediabetes. Although, the study does cover a significant period of time and is based in a real world setting, the lack of information about metformin dosage and compliance, diet and lifestyle influences and other medications, limits this conclusion. Further investigation is necessary based on the above mentioned factors.

CONSENT AND ETHICAL APPROVAL

The Ethics Committee of Isfahan University of Medical Sciences approved the protocol of this study (IR.MUI.MED.REC.1398.496) and the tenants of the Declaration of Helsinki were followed. All participants had provided written informed consents.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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