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Original Article

Study of the Predisposing Factors in Diabetic Patients with Hypoglycemia

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ABSTRACT

Background: Hypoglycemia is a serious complication of diabetes therapy and in diabetic patients it is considered the most important barrier in achieving tight glycemic control, it can lead to permanent brain damage and increased mortality if not treated on time.

Objective: This study aimed to study the risk factors and outcome in diabetic patients with hypoglycemia.

Patients and methods: A total of 200 diabetics with an average age of 54.44± 10.17 years, 156 of them were non-hypoglycemic [euglycemic] group and 44 were hypoglycemic age-matched and sex matched group. Venous plasma glucose levels, lipid profile, glycated hemoglobin [HbAIc] were measured in all diabetic patients and urine samples were assessed.

Results: There was an association between hypoglycemia and occurrence of nephropathy, reverse association between occurrence of hypoglycemia and use of metformin alone. Also, there was significant association between hypoglycemia and the use of Metformin + Sulfonylureas [SU] and use of insulin alone. Increasing age, smoking, self-monitoring of DM, non-use of metformin and use of insulin alone were shown as risk factors for hypoglycemia with univariate regression analysis.

Conclusion: Hypoglycemia is a complication of diabetes that cannot be ignored because it is associated with increased morbidity and mortality in diabetic patients. Advanced age, smoking and use of insulin were the common risk factors for hypoglycemia.

Keywords: Complication; Barrier; Mortality; Insulin.

INTRODUCTION

Hypoglycemia is one of the complications of diabetes mellitus [DM] that often occurs and causes effects for diabetic patients which is harmful. It can result in damage of the brain, mental change, and even life-threatening consequences. Hypoglycemia, according to American Diabetes Association [ADA], is defined as "any abnormally low concentration of plasma glucose that exposes the subject to potential harm" with a proposed threshold glucose value in the plasma <70 mg/dL [<3.9 mmol/L] [1,2]. Hypoglycemia in type-2 DM is less frequent than in type 1 DM [3]. The prevalence of severe hypoglycemia in type-1 diabetics is 0.2–3.2 episodes per patient per year, whereas in type-2 diabetics 0.1–0.7 per patient per year [4]. The overall event rate for severe hypoglycemia [requiring the assistance of another individual] in insulin-treated type-2 DM is approximately 30 percent of that in type 1 diabetes [5] and that event rates of hypoglycemia requiring professional emergency medical treatment range from 40 to 100 percent of those in type 1 DM [6].

Hypoglycemia is common in type 1 DM, especially in patients receiving intensive therapy of insulin in whom severe hypoglycemia risk is increased more than threefold. Less commonly, hypoglycemia may also affect type-2 DM patients who take insulin, sulfonylurea, or glinide [7]. Glyburide [glibenclamide] is more often associated with hypoglycemia than glipizide or glimepiride, probably because of the glyburide longer duration of action [8]. Severe hypoglycemia can occur during critical illnesses [9]. Among the drugs used to treat type 2 DM early in its course, insulin sensitizers [metformin, thiazolidinediones [TZD]], glucosidase inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, sodium-glucose co-transporter 2 inhibitors, and dipeptidyl peptidase-4 [DPP-4] inhibitors should not cause hypoglycemia [10]. Independent risk factors for hypoglycemia development included diabetes, septic shock, renal insufficiency, mechanical ventilation, severity of illness, and intensive insulin treatment to achieve tight glycemic control [11].

The hypoglycemia mechanism in chronic kidney disease [CKD] is less clear. It likely involves gluconeogenesis impairment, reduced insulin renal clearance, and reduced production of renal glucose. In severe liver failure, impaired gluconeogenesis is present [12]. The prevention of hypoglycemia involves risk factors assessment and treatment regimens tailoring to reduce risk. These principles include patient education and empowerment, self-monitoring of blood glucose frequently [SMBG], flexible and rational insulin [and other drug] regimens, individualized glycemic goals, and ongoing professional support and guidance [13]. Glycemic control can minimize retinopathy, nephropathy, and neuropathy risks in both type 1 and type 2 DM and may decrease cardiovascular disease risk. Target HA1C levels in patients with type 1 and 2 DM should be tailored to the individual, balancing the improvement in microvascular complications with hypoglycemia risk [14].

AIM OF THE WORK

This study aimed to investigate the predictors of hypoglycemia among patients with type-2 DM.

PATIENTS AND METHODS

This a cross-sectional study included 200 patients diagnosed with type-2 DM, 156 of them were non hypoglycemic and 44 were hypoglycemic [71 males and 129 females] with mean age of 53.5± 9.5 year for non-hypoglycemic and 57.6± 12.0 year for hypoglycemic group, selected from the Outpatient Clinics and Intensive Care Unit of Mansoura University Hospital, Faculty of Medicine, Egypt, from July 2019 to June 2021.Informed consents were obtained from all participants, and approval was given by the Institutional Research Board [IRB] of the faculty of medicine, Mansoura University by date 31/01/2019] code number MS.19.01.465]. Hypoglycemia was obtained retrospectively from the lab records of blood glucose results. The values of capillary glucose were used to identify the hypoglycemic group. Individuals with blood sugar less than 3.9 mmol/L [70 mg/dL] were included in the hypoglycemic group, whereas those who had readings equal to or greater than 3.9 mmol/L [70 mg/dL] were included in the non-hypoglycemic group. It was identified based on the ADA; it is defined when venous blood glucose levels reach <70 mg [2]. We **excluded** alcoholic, epileptic patients, patients with Liver failure, patients with end stage renal diseases, and Type 1 DM. Full history taking and clinical examination were taken from all participants. Blood pressure was taken in the sitting position using a random-zero sphygmomanometer. Fasting blood glucose [FBG] tested by spectrophotometric technique, lipid profile, 2-hour postprandial blood glucose, HbA1C, liver and kidney functions.

Specimen collection and preparation: Blood specimens were obtained and the usual precautions in the collection of venipuncture samples were followed strictly. After 8 hours fasting, three morning blood samples were drawn from all participants. First sample was dispensed in lavender top vacutainer tube containing EDTA for estimation of HAIC. Second sample was dispensed in grey top vacutainer tube containing sodium fluoride for measurement of FBG. Third sample was drawn in red top vacutainer tube without additives or anti-coagulants and then blood was allowed to clot for 15 minutes followed by centrifugation then serum was collected and refrigerated at temperatures of -80oC up to the time of measurement of lipid profile.

Investigations for identifying the complications were 1) Nervous system: Nerve conduction studies or CT brain; 2) Kidney affection: Serum urea, serum creatinine and urinary albumin; 3) Liver affection: Liver enzymes, albumin and bilirubin; 4) Ocular affection: Fundus examination or ophthalmoscope.

Statistical analysis: The SPSS software [version 27.0; IBM Inc, Chicago, IL, USA] was used for data entry and analysis. Data were tested for normal distribution using the Shapiro Walk test. Parametric quantitative data were expressed as mean ± SD [Standard deviation]. Qualitative data were represented as frequencies and relative percentages. Qualitative data for more than two groups were done by Chi-Square test [or Fisher's exact test]. For quantitative data use Student t-test to compare 2 independent groups and Mann-Whitney U test to compare 2 independent groups. Univariate and multivariate logistic regression analysis were used to test for dependent and independent risk predictor of a categorical outcome [Occurrence of hypoglycemia]. Fischer Exact test was used as correction for Chi-Square test when more than 25% of cells have count less than 5 in 2*2 tables. If p value ≤ 0.050, results were assessed as statistically significant

RESULTS

This study involved 200 patients with T2DM, 156 of them were non hypoglycemic and 44 were hypoglycemic. It was noticed that there was significant difference between the two groups regarding age [p=0.049], and smoking [p=0.041]as shown in **table [1].** There was no significant difference regarding all the tested parameters as shown in **table [2].** It was noticed that there was significant association between hypoglycemia and occurrence of nephropathy [p=0.022] as shown in **table [3].** It was noticed that there was significant reverse association between occurrence of hypoglycemia and use of metformin alone[p<0.001]. Also, there was association between hypoglycemia and the use of Metformin +SU [p=0.002] and use of insulin alone [p<0.001] as shown in **table [4].** It was noticed that there was no significant difference between the type of insulin therapy and the occurrence of hypoglycemia as shown in **table [5].** It was

noticed that increasing age, smoking, self-monitoring of DM, non-use of metformin and use of insulin alone were shown as risk factors for hypoglycemia with univariate regression analysis. However, with multivariate regression analysis, smoking, self-monitoring of DM, non-use of metformin and use of insulin alone were shown as independent risk factors for hypoglycemia as shown in **table [6].**

Table [1]: Characteristics of the studied diabetic patients

		Not hypoglycemic [n= 156]		Hypoglycemic [n= 44]		Test value	p- value
		N	%	N	%		
Age [years]	Mean± SD	53.5± 9.5		57.6± 12.0		1.97	**0.049***
Gender	Male	50	32.1%	21	47.7%	3.68	0.055
	Female	106	67.9%	23	52.3%		
Marital status	Single	4	2.6%	1	2.3%	2.76	0.430
	Married	109	69.9%	31	70.5%		
	Widow[ers]	8	5.1%	5	11.4%		
	Divorced	35	22.4%	7	15.9%		
Residency	Urban	43	27.6%	6	13.6%	3.72	0.156
	Rural	21	13.5%	8	18.2%		
	Not known	92	59.0%	30	68.2%		
Smoking		12	7.7%	8	18.2%	4.196	**0.041***
Educational level	Illiterate	80	51.3%	29	65.9%	3.114	0.128
	Primary education	36	23.1%	7	15.9%		
	Secondary education	30	19.2%	7	15.9%		
	University	8	5.1%	1	2.3%		
Occupation	Unskilled	108	69.2%	32	72.7%	0.682	0.711
	Skilled	46	29.5%	12	27.3%		
	Professional	2	1.3%	0	0.0%		

SD: standard deviation; *: Statistically significant [p≤ 0.05]

Table [2]: Clinical and biochemical characteristics of the study groups

		Not hypoglycemic [n= 156]		Hypoglycemic [n= 44]		Test value	p- value
		N	%	N	%		
Duration of diabetes [years]	Mean± SD	9 [1-18]		7 [1-16]		0.295	0.768
Age at diagnosis [years]	Mean± SD	42.4 ± 9.9		46.4 ± 10.8		2.31	0.136
Family history of DM		74	47.4%	14	31.8%	3.397	0.065
Hospitalization due to DM complications		50	32.1%	18	40.9%	1.2	0.273
Self-monitoring blood glucose		36	23.1%	15	34.1%	3.415	0.106
Hypertension		99	63.5%	30	68.2%	0.334	0.563
SBP [mmHg] [Mean± SD]		129.3 ± 15.6		130.2 ± 15.0		0.363	0.716
DBP [mmHg] [Mean± SD]		82.6 ± 9.0		83.2 ± 8.3		0.386	0.699
HbA1C [%] [Mean± SD]		7.38 ± 2.84		6.81 ± 1.76		1.843	0.076

SD: standard deviation, SBP; systolic blood pressure, DBP; diastolic blood pressure, HbA1c; hemoglobin A1c.*: Statistically significant [p≤ 0.05]

Table [3]: Comparison between hypoglycemic and non- hypoglycemic groups regarding DM complications.

Parameters	Not hypoglycemic [n= 156]		Hypoglycemic [n= 44]		Test value	p- value
	N	%	N	%		
Cardiovascular complications	11	7.1%	5	11.4%	0.867	0.352
Cerebrovascular complication	11	7.1%	1	2.3%	1.39	0.238
PAD	85	54.5%	23	52.3%	0.819	0.365
Retinopathy	56	35.9%	20	45.5%	1.33	0.249
Nephropathy	3	1.9%	4	9.1%	5.1	**0.022***
Neuropathy	117	75.0%	36	81.8%	0.887	0.346

PAD; peripheral arterial disease; *: Statistically significant [p≤ 0.05]

Table [4]: Comparison between hypoglycemic and non- hypoglycemic groups regarding DM management therapy.

Parameters	Not hypoglycemic [n= 156]		Hypoglycemic [n= 44]		Test value	p- value
		%	N	%		
Diet alone	14	8.9%	1	2.3%	1.428	0.194
Metformin alone	28	17.9%	0	0.0%	12.946	**<0.001***
Metformin +SU	18	11.5%	10	22.7%	7.465	**0.002***
Metformin+ SU+ TZD	20	12.8%	10	22.7%	6.847	**0.005***
Metformin +Incretins	7	4.5%	0	0.0%	1.106	0.288
Insulin alone	26	16.7%	14	31.8%	10.542	**<0.001***
Insulin + Metformin	43	27.6%	9	20.5%	1.966	0.122
Statins	66	42.3%	19	43.2%	0.358	0.760
Antihypertensive	99	63.5%	30	68.2%	0.334	0.563
ACE inhibitors	11	11.1%	6	20%	2.348	>0.05
Alpha blockers	17	17.2%	3	10%		
ARBs	15	15.2%	4	13.3%		
Beta blockers	10	10.1%	6	20%		
CCBs	29	29.3%	7	23.3%		
Diuretics	17	17.2%	4	13.3%		

*: Statistically significant [p≤ 0.05], ACE inhibitors; Angiotensin Converting Enzyme, ARBs; Angiotensin-receptor blockers, CCBs; calcium channel blocker SU; Sulfonylureas, TZD; Thiazolidinediones

Table [5]: Comparison between hypoglycemic and non- hypoglycemic groups regarding type of insulin therapy

	Not hypoglycemic [n= 156]		Hypoglycemic [n= 44]		Test value	p- value
	N	%	N	%		
Mixed insulin	**[n= 50]**		**[n= 16]**			
Premixed insulin [Mixtard]	34	68.0%	12	75.0%	1.688	0.172
Mixed manually	16	32.0%	4	25.0%		
Regular insulin	**[n= 19]**		**[n= 7]**			
Regular insulin alone	10	52.6%	5	71.4%	2.110	0.124
Regular insulin as a basal bolus	9	47.4%	2	28.6%		

*: Statistically significant [p≤ 0.05].

Table [6]: Univariate and multivariate regression analysis of risk of hypoglycemia [n= 44]

	Univariable				Multivariable			
	p	OR	95.0% CI		*p*	OR	95.0% CI	
Age	**0.043***	1.075	1.002	1.153	0.286	1.042	0.966	1.124
Female gender	0.605	1.140	0.694	1.871				
Duration of DM	0.152	0.403	0.162	1.007				
Family history of DM	0.317	0.898	0.728	1.108				
Hospitalization due to previous complications	0.409	1.074	0.989	1.132				
Smoking	**0.037***	1.645	1.167	2.798	0.053	1.702	0.993	2.918
Self-monitoring of DM	**0.117**	1.879	0.490	1.976				
HTN	0.638	1.023	0.930	1.127				
HBA1C	0.696	0.977	0.868	1.099				
Metformin therapy	**<0.001***	0.548	0.246	0.861	**<0.001***	0.615	0.334	0.894
Insulin therapy	**<0.001***	3.633	2.019	6.539	**<0.001***	3.402	1.877	6.166

OR: Odd's ratio, CI: confidence interval, HbA1c; hemoglobin A1c, HTN; hypertension*: DM; diabetes mellitus, statistically significant [p< 0.05]

DISCUSSION

The current study was conducted to study the risk factors and outcome in patients with hypoglycemia. We focused on the evaluation of: [i] the incidence rate of hypoglycemia; and [ii] patient- and drug-related factors associated with hypoglycemia. The present study was a cross-sectional study conducted on 200 patients with type 2 DM, 156 of them were non hypoglycemic and 44 were hypoglycemic recruited from Mansoura university hospitals. The mean age of hypoglycemic group was 57.6± 12.0 years which is near to the results by Paul et al that showed that more than half of the patients were aged 60 years or older [15]. The elderly patients are at increased risk of hypoglycemia due to renal function deterioration which affecting drug clearance, adverse drug interactions resulting from polypharmacy of the elderly, and cognitive functioning impairment [16].

This study disagrees with the studies done by **Alghamdi *et al.*** and **Kagansky *et al*.**[17,18] who showed no link between age and hypoglycemia.

We also found that there was no association between gender and hypoglycemia. Also, **Alghamdi et al.** [17] agreed with our results, although other studies as **Kagansky *et al.*** and **Arabi *et al.*** [18,19] reported that females had a higher chance of developing hypoglycemia as compared to males.

In the current study, the incidence of smoking was higher in the hypoglycemic group. This agreed with **Ismail *et al.*** and **Szwarcbard *et al.***[20,21] who stated that smokers showed higher rate of severe hypoglycemia than nonsmokers. The most profound impact of smoking is associated with insulin sensitivity. **Whalen KL, Stewart, Duan *et al.* and Severino et al** [22,23,24] stated that smoking decreases insulin subcutaneous absorption, resulting in increased dosing requirements. This behavior may also alter the pathogenesis of early steps in insulin action, such as signal transduction and transport of glucose, increasing micro-and macrovascular complications risk in patients with DM. Also, **Bott *et al.*** [25] stated that the relation of smoking to severe hypoglycemia may also be attributed to the effect of smoking on clearance of insulin, leading to hyperinsulinemia, increasing postprandial hypoglycemia risk, and metabolic control worsening.

The present study showed no significant difference between the studied groups regarding occupation, education, residency and marital state. Contrarily, **AlKhaldi *et al.*** [26] showed that intermediate/university education patients reported more hypoglycemia than other educational levels.

Our study confirmed that there was association between hypoglycemia and occurrence of nephropathy. In line with our finding, **Moen *et al.*** [27] showed that diabetics who have CKD have a higher hypoglycemia frequency than patients with diabetes who do not have CKD. Reasons for this increased risk include reduced requirements of insulin because of decreased renal insulin clearance, decreased insulin degradation in peripheral tissues, reduced gluconeogenesis in the kidney due to a reduction in renal mass, and in CKD there is prolonged half-life of other drugs. Also, studies of **Holstein *et al.* and Davis *et al.*** [28,29] confirmed that renal impairment is a further independent hypoglycemia risk factor.

In the current study, the incidence of hypoglycemia was higher in cases used Metformin+SU, Metformin+ SU+ TZD and insulin. Therefore, in hospitalized patients, the anti-diabetic medication should be adjusted according to the nutritional status of patients. This comes in agreement with **Heald *et al*.** and **Miller *et al.*** [30,31] who reported that patients treated with sulphonylureas or insulin are particularly associated with increased likelihood of hypoglycemia. This also agreed with **Torimoto *et al.*** [32] who showed that the rate of insulin use was significantly higher in the hypoglycemia group than in the nonhypoglycemia group, and **Bullano *et al.*** [33] reported that the most common predictor for hypoglycemia risk in diabetics is insulin. Also, **Paul *et al.*** [15] showed that the majority of episodes of hypoglycemia experienced by diabetics are related to medications. **Donnelly *et al.*** [34] demonstrated that ~45% of insulin-treated T2DM patients had a hypoglycemic event and 2% of which were severe; moreover, previous history of hypoglycemia and insulin treatment duration were significant predictors. The results are consistent also with those of **Henderson *et al.*** [35] as 73% of the study patients had experienced hypoglycemia since commencing insulin, the frequency of which

increased with diabetes duration and was inversely related to current HbA1c.

We did not find that the use of β-blockers, alpha blockers, Angiotensin Converting Enzyme [ACE] inhibitors, Angiotensin-receptor blockers [ARBs], calcium channel blocker [CCBs], diuretics was associated with severe hypoglycemia. This correlates with the result of **Davis *et al.*** [29] who did not find that the β-blockers use was associated in either univariate or multivariate analyses with severe hypoglycemia. This was not matching with **Elshimy *et al.*** [36] who reported that ACE-inhibitors are hypothesized to cause hypoglycemia by increasing insulin sensitivity, and leading to muscles vasodilation with increased muscle glucose uptake.

The present study revealed that there was no significant difference between hypoglycemic and non- hypoglycemic groups regarding HbA1c level, blood pressure, family history of diabetes, hospitalization due to diabetes complications and SMBG. This is consistent with results of **Davis *et al.*** [29] that showed that higher HbA1c levels should not be regarded as a high risk of severe hypoglycemia. Also **Cariou *et al.*** [37] observed that HbA1c level was not predictive of hypoglycemia in either T1DM or T2DM. Also **Munshi *et al.*** [38] showed that HA1c levels in older population are not associated with risk of hypoglycemia in type-2 DM patients on insulin therapy. Higher HA1c goals do not protect against hypoglycemia.

This was in contrast to the study conducted by **Ibrahim and Nesma**[39] as they showed that the HBA1c was significantly higher in the group with hypoglycemia. The association between HbA1c and hypoglycemia risk is complex, partly because HbA1c reflects the average glycemic control over period of 3-month and does not convey glycemic variability and excursions. **Malkani and Kotwal** [40] have suggested that low HbA1c may predict hypoglycemia risk in type 1 but not type 2 DM. While **Duckworth et al.** [41] stated that the rates of hypoglycemia were higher among patients with type 2 DM achieving low HbA1c targets with intensive glucose-lowering therapy, **Zoungas *et al.*** [42] stated that the episodes of hypoglycemia may be the result of intensive treatment and polypharmacy rather than low levels of glycemia themselves.

Ly *et al.* [6] stated that the HbA1c and severe hypoglycemia relationship was U shaped, and the association became less significant once other key patient- and treatment-related factors were taken into consideration [specifically, patient age, sex, comorbidities, polypharmacy, diabetes medications used, prior hypoglycemia history]. **Wang *et al.*** [43] reported different associations between SMBG and glycemic control in patients diagnosed with T2DM recently and in T2DM patients with long-term follow up. SMBG was associated with higher detection of episodes of hypoglycemia in both study populations.

In the current study, the use of regular insulin alone was higher in the cases with hypoglycemia, while the use of regular insulin as a basal bolus was higher in the non-hypoglycemic group, however, the difference didn't reach a statistically significant level. This matches to results of **Alghamdi *et al.*** [17] that patients during hospitalization on supplemental insulin [sliding scale or corrective dose] had a lower chance to have hypoglycemia, whereas those who were given basal insulin or were treated by multiple daily injections had almost double the risk. **Vague *et al.***[44] demonstrated that hypoglycemia risk was 22% lower with insulin detemir than with neutral protamine Hagedorn [NPH] insulin and 34% lower for nocturnal hypoglycemia . Nightly plasma glucose profiles were smoother and more stable with insulin detemir.

In the current study with univariate regression analysis, increasing age, smoking and use of insulin was associated with increasing risk for hypoglycemia while the use of metformin was lower risk for hypoglycemia. With multivariate regression analysis, use of insulin was the independent risk factor for increasing risk for hypoglycemia while the use of metformin was an independent risk factor for decreasing the risk for hypoglycemia, therefore old aged and smokers must be observed and protected against hypoglycemia. In the same line, **AlKhaldi *et al.*** [26] displayed that; young age, type-1 DM, long duration of DM, insulin use could be considered as risk factors for hypoglycemia development. This agreed with **Ikeda *et al.*** [45] who showed that the major predictors of severe hypoglycemic events were age and current use of insulin and/or SU. **Geller *et al.*** [46] showed that the most frequently administered drug in patients with severe hypoglycemic episodes were insulin [60.8%] and SUs [33.1%]. **Hashikata *et al.*** [47] also showed that hypoglycemia occurs in elderly patients more frequently and in patients using insulin and SUs; however, it remains uncertain whether dosage of SU is associated with the frequency of hypoglycemic events. **Miller *et al.*** [48] reported that increased severe hypoglycemia risk in female patients, black or African-American patients and older patients. **Bruderer *et al.*** [49] identified that age and sulfonylurea use as risk factors for severe hypoglycemia, together with renal failure and cognitive impairment/dementia. With regard to smoking, **Hirai *et al.*, Jensen *et al.* and Sari *et al.***[50-52] have demonstrated that smoking was associated with a higher possibility of hypoglycemia particularly in type I DM.

Concerning metformin mediated hypoglycemic, a novel research conducted by **Joseph** [53] was in disagreement with the current study as he reported in a case report that a patient developed symptomatic hypoglycemia while being treated with a therapeutic dose of metformin. Although advised to be taken with meals to avoid gastrointestinal upset, patients should also be educated to take metformin with meals to reduce the risk of metformin-associated hypoglycemia.

A case reports of **Jacob *et al.*** [54] estimating no more than 2% rate of hypoglycemia secondary to metformin overdose or toxicity, but hypoglycemia at a therapeutic metformin dose is thought to be rare. Several hypotheses have been proposed for metformin-induced hypoglycemia, but are currently controversial. Metformin-induced hypoglycemia hypotheses include a direct link to its mechanism of action, as decreased hepatic glucose production and decreased glucose absorption. **Elshimy *et al.*** [36] reported that combination of ACE-inhibitor with 1 or more oral hypoglycemic agents, including metformin, is thought to increase the risk of hypoglycemia. However, the risk does not appear to be significant, as ACE-inhibitors in combination with metformin is commonly prescribed in type 2 DM due the ACE-inhibitors' protective benefits towards diabetic nephropathy. Also, a recent study of **Niveen *et al.*** [55] about the ACE-inhibitors and ARBs with metformin and other oral hypoglycemics revealed no drug-drug interaction causing hypoglycemia [instead, it showed significant increase in total cholesterol and low-density lipoprotein]. A pharmacy review update of **Triplitt** [56] about medications commonly prescribed in the management of type-2 diabetes mellitus also did not report any hypoglycemic risk with ACE-inhibitors, nor a significant drug-drug interaction between metformin and ACE-inhibitors

The current study had some limitations as it has a small sample size and being a single center study which decrease the power of the obtained results. We did not search for the presence of hypoglycemia unawareness in these patients. The potential cardiovascular, neurogenic, psychological, and socioeconomic adverse effects of hypoglycemia were also beyond the scope of this study.

Conclusion: Hypoglycemia is a complication of diabetes that cannot be ignored because it is associated with increase morbidity and mortality in diabetic patients. Increasing age, smoking and use of insulin were the common risk factors for hypoglycemia reported in the current study. Individualized glycemic target, judicious use of ant diabetic drugs,

appropriate lifestyle and dietary habit, and SMBG should be implemented in all patients with diabetes for hypoglycemia avoidance.

Recommendation: A larger, prospective study is required to confirm these findings. Further studies with larger sample size should be carried out including cases from more than a single center. Patient-centered multidisciplinary care may help proactively identify at-risk patients and address the multiplicity of factors contributing to occurrence of hypoglycemia.

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