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Comparing the incidence of hypoglycemia episodes in patients with type 2 diabetes and chronic kidney disease treated with insulin or glibenclamide

ABSTRACT

Introduction. Hypoglycemia is one of the side effects of glibenclamide, which is administered orally in people with diabetes. Hypoglycemia may occur easily due to the reduced metabolism of this drug in patients with chronic kidney disease. The aim of this study was to compare the incidence of hypoglycemia in patients with chronic kidney disease who were treated with glibenclamide or insulin.

Material and methods. In this study, 87 patients with type 2 diabetes and in stage 3–4 of chronic kidney disease (CKD) were examined. The patients were divided into two groups of glibenclamide (N = 44) and insulin (N = 43) based on the type of blood glucose-lowering therapy. Next, demographic data, serum creatinine level, number of hypoglycemic episodes over the last year and the amount of consumed drugs were recorded in the checklist. Finally, the data analysis was performed using the SPSS Software.

Results. There was no significant difference between the two groups in terms of age, estimated glomerular filtration rate (eGFR), weight, duration of diabetes and blood glucose control. In addition, it was indicated that 38% of patients in the glibenclamide group and 32% of patients in the insulin group had at least one hypoglycemic episode. Also, in those two groups, there was no significant correlation between doses of the drug and the number of hypoglycemic episodes.

Conclusions. This study showed that there was no significant difference between the patients with chronic kidney disease who were treated with insulin and those patients who were treated with glibenclamide in terms of number of symptomatic hypoglycemic episodes. (Clin Diabetol 2018; 7, 3: 159–163)

Key words: glyburide, kidney disease, chronic, insulin, hypoglycemia, diabetes mellitus

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Introduction

Diabetes is the most common endocrine disorders in the world and its prevalence is rising (in 1980, 4.7% of individuals over the age of 18 were afflicted with diabetes but the latter percentage increased up to 8.5% in 2014). In 2015, it was estimated that 1.5 million deaths were directly caused by diabetes. In 2012, 2.2 million deaths were associated with high blood glucose [1].

The renal failure is one of the complications of diabetes and several studies indicate that the primary cause of renal failure is diabetes among 25% of patients with renal failure and 50% of patients with end stage renal disease (ESRD) [2, 3]. It is impossible to prevent the progression of renal failure and other complications of diabetes, except by controlling the blood glucose in these patients. Many patients tend to get oral glucose-lowering drugs. According to the National Health and Nutrition Examination Survey, 62.9% of patients with CKD stages 4–5 receive at least one oral glucose-low-

ering drug [4]. The metabolism of many drugs widely used in the treatment of diabetes is dependent on the kidney. As a result, these drugs are contraindicated or they require dose adjustments to prevent hypoglycemic episodes, lactic acidosis and other possible complications. Besides, review studies and guidelines do not adopt any definite approach towards using these drugs [5]. As such, the clinical opinions of physicians are different in the use of these drugs. A study was conducted on 301 patients in stage 3 to stage 5 of CKD and the results indicated that, based on the guideline on chronic kidney disease patients [6], 53% of them took drug or doses outside of the proposed recommendation, of which 24.4% were treated with the glibenclamide [7]. Another study was conducted in France and it was found that the general practitioners and diabetes specialists did not take into account the proposed recommendations and, thus, they prescribed metformin for 63% of patients with stage 3 of CKD and 33% of patients with stage 4 of CKD. Also, they prescribed sulfonylureas for 51% and 61% of patients with stage 3 and stage 4 of CKD, respectively [8].

As noted, sulfonylureas are among the drugs that are used regardless of proposed recommendations. Although these drugs are involved in controlling blood glucose by stimulating the secretion of insulin, the same mechanism can put patients at increased risk for hypoglycemia. Actually, the risk of hypoglycemia increases in patients who have decreased level of GFR. The cause of this increased risk in patients with renal failure can be summarized as follows: 1) decreased level of insulin clearance and the oral drug itself [5] and 2) decreased level of gluconeogenesis due to loss of kidney mass [9]. For this reason, many researchers have forbidden the use of glibenclamide in patients with chronic kidney disease stages 3–5 [10].

Considering the refusal of many patients to accept insulin therapy and the costly use of existing oral drugs in the treatment of renal failure, many patients still tend to use these drugs, despite being aware of the side effects of oral drugs such as glibenclamide. Accordingly, the aim of this study was to compare the prevalence of hypoglycemia in patients with renal failure who were treated with glibenclamide and patients who received insulin.

Materials and methods

The study was conducted in a historical cohort design. As such, the medical records of all diabetic patients in stage 3 and stage 4 of CKD, who were referred to nephrology clinics from March 21, 2011 to September 21, 2015 in Qom province, were reviewed. In total, the medical records of 107 patients treated with glibenclamide or insulin were extracted. Next, the medical records of patients that were followed for at least 1 year to control the blood glucose and were checked up at least for 10 sessions during this period were selected. As such, other medical records were excluded from the study. Finally, 87 medical records were included in the study based on the entry criteria for the study. The medical records of 20 other patients were also examined. According to available data and after contacting the patients, it was found that there was no significant difference between these 20 medical records and the 87 medical records in terms of hypoglycemia occurrence.

Those patients who presented with renal failure for at least 3 months or more were diagnosed as CKD patients. Accordingly, all patients who were at stage 3 of CKD or higher were included in the study. Besides, the patients' GFR was calculated using the Cockcroft--Gault formula based on gender, weight, age and serum creatinine (GFR={((140–age) × weight)/(72 × SCr)} × 0.85 (if female)).

Furthermore, the patients' medical records were investigated in terms of demographic variables, type of diabetes treatment and incidence of hypoglycemia. Given the one-year follow up, it was attempted to make use of neurological and neuroglycopenic symptoms as well as patients' remarks in order to determine the incidence of hypoglycemia. Hypoglycemia episode is defined as an event with symptoms of hypoglycemia which was associated with a blood glucose level below 50 mg/dL or prompt recovery after oral carbohydrate ingestion or intravenous glucose administration.

All patients were informed about the side effects of medications and hypoglycemia symptoms at the onset of their treatment, and in each visit they were asked about hypoglycemia symptoms and episodes.

Having collected the required information, all the data was analyzed using the SPSS Statistical Software (Version 22). Regarding the quantitative variables, it was decided to calculate the mean and standard deviation. Given the qualitative variables, it was endeavored to calculate the absolute and relative frequency. In this analysis, frequency distribution and prevalence indices as well as statistical T-test and Chi-Square Test with a significant level of less than 0.05 were used. In addition, the logistic regression was implemented to investigate the impact of forenamed factors, such as type of treatment, on hypoglycemia. Finally, the Spearman correlation coefficient was used to check the correlation between the drug dose and number of episodes.

The information was extracted confidentially and the results were announced in a group-based format. Patients were fully aware of complications of gliben-

Table 1. Distribution of patients according to the type and dose of treatment

Treatment	Frequency	Percent	Cumulative percent
Glibenclamide (5 mg)	13	14.9	14.9
Glibenclamide (7.5 mg)	5	5.7	20.6
Glibenclamide (10 mg)	8	9.2	29.8
Glibenclamide (12.5 mg)	1	0.1	29.9
Glibenclamide (15 mg)	6	6.9	36.8
Glibenclamide (20 mg)	11	12.6	49.4
Insulin	43	50.6	100

clamide, but their unwillingness to use insulin led the researchers to treat them with glibenclamide.

Results

In this study, 87 diabetic patients in stage 3 and 4 of CKD were studied. In fact, 43 patients were treated with insulin and 44 patients received glibenclamide. Table 1 shows the distribution of patients according to the type and the dose of treatment. The patients were divided into two groups of glibenclamide (N = 44) and insulin (N = 43) based on the type of blood glucose-lowering therapy.

It was found that, except for the gender based distribution, there was no significant difference between the two groups regarding the study variables (age, GFR, weight and duration of diabetes). Besides, it was found that there was no significant difference in blood glucose control between two groups of patients (Tab. 2).

It was indicated that 17 patients (38.6%) in the glibenclamide treated group and 14 patients (32.6%) in the insulin treated group experienced symptomatic hypoglycemia within a one-year of follow up. However, the findings indicated that the difference was not statistically significant ($p = 0.557$). This study showed that there was no significant difference between the two groups in terms of number of hypoglycemic episodes. The mean number of hypoglycemic episodes in the glibenclamide-treated and insulin-treated groups were 1.89 ± 1.33 and 1.98 ± 1.61 ($p = 0.776$) respectively.

No correlation was found between glibenclamide dose ($r = 0.103$, $p = 0.504$) or insulin dose ($r = 0.124$, $p = 0.253$) and the number of hypoglycemic episodes based on the result of the Spearman correlation coefficient.

The logistic regression showed that, among the variables studied in this study, there was only a significant relationship between patients' age and incidence of hypoglycemia (Tab. 3).

Discussion

This study was conducted due to observation thaat patients with renal failure are willing to use glibenclamide in spite of its most important complication, hypoglycemia. Despite the contraindication to use

Table 2. Comparison between the two groups regarding the under study variables

Variable	Glibenclamide group	Insulin group	p-value*
Male to female ratio	2.76	1.05	0.038
Age (year), mean ± SD	69.02 ± 9.77	64.58 ± 17.48	0.146
Weight [kilogram], mean ± SD	75.73 ± 12.16	75.37 ± 14.6	0.902
Diabetes duration (year), mean ± SD	13.43 ± 8.33	15.1 ± 10.52	0.360
GFR [mL/min/1.73 m^2], mean ± SD	35.57 ± 16.37	31.82 ± 15.95	0.282
FBG [mg/dL], mean ± SD	110.02 ± 61.4	120.07 ± 77.4	0.547
HbA_{1c} (percent), mean ± SD	5.54 ± 3.66	5.32 ± 3.67	0.774

*P-value with 2-tailed, unpaired t-test. FBG — fasting blood glucose

Table 3. Effects of study variables on hypoglycemic episode by logistic regression

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Treatment type (glibenclamide)	0.039	0.478	0.007	1	0.936	1.039	0.408	2.651
Gender (male)	0.457	0.502	0.831	1	0.362	1.580	0.591	4.224
Age (year)	0.046	0.024	3.857	1	0.050	1.048	1.000	1.097
GFR [mL/min]	0.005	0.015	0.095	1	0.757	1.005	0.976	1.034
Constant	–4.229	1.815	5.429	1	0.020	0.015		

S.E. — standard error; df — degrees of freedom; Sig. — significance

glibenclamide in patients with CKD (Stage 3 onwards), many patients do not accept insulin therapy due to problems they face in using such a drug. On the other hand, oral antidiabetic drugs used in renal failure are either not available or at a higher cost. The results of this study indicated that many patients still tended to use these drugs, despite being aware of the side effects of oral drugs such as glibenclamide. Similarly, previous studies have shown that 18% to 61% of patients in stage 3 and higher stages of CKD have been treated with sulfonylureas, which has been a forbidden practice [7, 8, 11].

This non-compliance with the guidelines can be attributed to different reasons. In some studies, part of this lack of compliance was attributed to physicians' lack of knowledge and information. However, in the present study, the physicians and patients were aware of the contraindications to the drug use. Other causes have also been mentioned in studies; for example, patients argue that oral drugs are effective and easier to use and, unlike insulin, the oral drugs do not require daily doses adjustment. Insulin administration is associated with high risk of hypoglycemia in patients with renal failure [9, 12, 13].

The results of this study did not show a significant difference between insulin treated and glibenclamide treated groups in terms of incidence of symptomatic hypoglycemia. However, previous studies have shown different results in this regard. Studies conducted on diabetic patients with normal kidney function have reported hypoglycemia rates between 0.2 and 1.8 in return for 100 person-years among users of sulfonylurea [14–16]. Regarding the other five studies that examined hypoglycemia caused by sulfonylureas in patients with renal failure, it was indicated that one study, similar to the present one, did not show any association between glibenclamide consumption and hypoglycemia [17]. However, the other four studies showed that the risk of hypoglycemia was higher in patients who used sulfonylureas than those patients who used other drugs [18–20].

Van Dalem et al. showed that there was an association between using sulfonylureas and the risk of hypoglycemia. Actually, the incidence rates of hypoglycemia in patients who have just started taking drug and those who have recently started taking the drug were 13.5 in 1000 person-years and 4.6 in 1000 person-years, respectively. Besides, they found that the incidence rate of hypoglycemia in patients who already took drug was 0.6 in 1000 person-years [21]. Given the present study, it was indicated that since all patients were already treated with these drugs, the difference between the present study and the rest of the studies could be attributed to the former reason.

There are some evidences that argue that sulfonylureas should not be used in patients with chronic kidney disease stage 3–5. For example, researchers believe that the risk for hypoglycemia is high in patients with renal failure because these patients are characterized with reduced clearance of sulfonylureas and insulin. On the other hand, due to decreased level of renal gluconeogenesis, these patients can deal with hypoglycemia to a lesser extent and power. Also, reduced level of appetite caused by uremia can also increase the risk of hypoglycemia in these patients [17, 22–24]. Furthermore, studies have shown that severe hypoglycemia can debilitate the prognosis of these patients in that the mortality rate of patients who once experienced severe hypoglycemia is 1.4 times more than that of the rest of the patients [25]. Also, the risk of death is very high over 90 days after a severe hypoglycemic attack [26].

Conversely, there are some evidences (e.g. the results of the present study) that undermine the absolute ban on using sulfonylureas (e.g. glibenclamide) in patients in stage 3 of CKD and higher. Weir et al. undertook a nested case-control study and found that there was no relationship between renal failure and the risk of hypoglycemia caused by glibenclamide [17]. Interestingly, the studies that showed that there was a relationship between death and hypoglycemia could not prove that the latter relationship was a causal one [27]. Besides, the pharmacokinetic studies conducted on glibenclamide showed that there was no correlation between creatinine clearance (29–131 ml/min/1.73 m^2) and glibenclamide clearance [28].

Conclusions

Regarding the findings of this study and the results of similar recent studies on such oral glucose-lowering drugs as glibenclamide, it can be argued that the ban on using sulfonylureas in CKD of stage 3 onwards can be revised.

It seems that failure to compare the severity of hypoglycemia in the two groups and the lack of investigation of patients' survival can be considered among the limitations of this study. Thus, it is suggested that further studies can be conducted on this subject. If this misleading belief is rejected, the physicians can prescribe glibenclamide as a cheap and less side effect drug in many diabetic patients who are diagnosed with chronic kidney disease caused by diabetic nephropathy.

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Conflict of interest

None declared.

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