The Professional Medical Journal
www.theprofesional.com
DOI: 10.17957/TPMJ/16.2669

ORIGINAL PROF-2669

DIABETIC NEPHROPATHY;
TO FIND OUT THE FREQUENCY OF HYPOGLYCEMIA IN THESE PATIENTS

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Article received on:
30/01/2015
Accepted for publication:
22/01/2016
Received after proof reading:
09/02/2016

ABSTRACT… Objectives: To find out the frequency of hypoglycemia in patients with diabetic nephropathy. **Study Design:** Cross sectional study. **Setting:** Emergency department and department of medicine Liaquat university Hospital Hyd/ Jamshoro. **Study Period:** One year from 01-03-2009 to 28-02-2010. **Methodology:** Two hundred cases of diabetic nephropathy on the basis of symptoms and signs of hypoglycemia were selected in this study. **Results:** Out of 200 patients, 102(51%) were males and 98(49%) were females, 10.5% had type-1 diabetes and 89.5% had type-2 diabetes. Most of the patients belonged to 60 to 75 years of age. The average duration of diabetes was 12.20 ± 6.14 years. Out of 23 hypoglycemic patients, 5 (21.7%) had type-1 diabetes in which 4 were male and one was female while 18 (78.3%) had type-2 diabetes in which 10 were male and 8 were female patients. **Conclusion:** It was observed that hypoglycemia was common in diabetic patients, who developed renal failure due to diabetic nephropathy.

Key words: Diabetes mellitus, Nephropathy, Renal failure, Hypoglycemic

Article Citation: Liaquat J, Bawany MA, Shaikh N, Khahro AA, Naz F. Diabetic nephropathy; to find out the frequency of hypoglycemia in these patients. Professional Med J 2016;23(2):121-128. **DOI:** 10.17957/TPMJ/16.2669

INTRODUCTION

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia due to relative insulin deficiency, resistance, or both.[1]

As a minimum one hundred seventy even million population suffered by diabetes through world or 2.8% of the population and it is estimated that by the year 2030, this number will almost double. DM happen worldwide, however no is most frequent, particularly type-2 in the more developing national states. High incidence is, conversely, predictable to presence in the Africa and the Asia, wherever commonly cases will possibly reported by 2030.[2]

Diabetes mellitus encompasses a family of disorders of carbohydrate metabolism that are characterized by hyperglycemia in the development of long-term neuropathic, microvascular and macrovascular complications.[3]

DN is a collection of the symptoms of albuminuria, GFR, AH and greater risk of cardiovascular disease. Increased level of the glucose in the blood and the associated microvascular illness is linked to the kidneys damage development. The damage becomes detectable when protein (albumin) is excreted in the urine in higher concentration than normal.[4] Hence, albuminuria is the earliest and most sensitive indicator of the diabetic nephropathy. When the albumin in the urine is low. (20-200 μg/min), or30-300mg/day, the condition is known as microalbuminuria or incipient nephropathy, higher albumin excretion is called macro albuminuria or overt proteinuria.[5] Eventually the condition can lead to renal failure.

Diabetic nephropathy affects 20% to 40% of both type-1 and Type-2 diabetic patients.[6] Diabetics mostly type-2, account for one third of all patients requiring renal replacement therapy in western countries.[7] Diabetic nephropathy is more common in population of the Asian descent than in whites. The prevalence of microalbuminuria is twofold andmacroalbuminuria threefold greater in Asians than in whites.[8] Other micro vascular complications such as retinopathy usually proliferative, almost always accompany diabetic

nephropathy and tends to deteriorate as renal failure progresses.[9]

Majority of patients with the failure of the kidneys by the DN are controlled on insulin. The kidneys metabolize most of oral hypoglycemic agents and they tend to accumulate during renal failure causing the risk of hypoglycemia and toxicity. Many specialist centers prefer to transfer all patients receiving oral hypoglycemic agents to insulin when serum creatinine concentration reaches 200μmol/L (2.4mg/dl).[10]

Like as development in the renal failure, clearance of the insulin and the decreased dehydration due to the kidneys. The insulin sensitivity and insulin secretion is also decreased and decreased insulin requirement is also seen in the diabetic patients who develop acute renal failure.[11] Study conducted in type-1 diabetics with diabetic nephropathy has shown increased insulin levels and decreased insulin requirements.[12] Frequent blood glucose monitoring is required to decide any change in the insulin regimen in patients with diabetic nephropathy. Insulin requirement may decrease as kidneys are the site for insulin degradation; furthermore, glucose lowering medications (sulfonylurea and metformin) are contraindicated in advanced renal insufficiency.[13] In our clinical experience diabetic patients suffering from chronic renal failure require less insulin or oral hypoglycemic drugs for optimal glycaemic control. If the dosage of insulin or oral hypoglycemic drugs is not regulated properly this can lead to hypoglycemic episodes or poor metabolic control.

MATERIAL AND METHODS

This cross sectional study was conducted at Emergency department and department of medicine Liaquat university Hospital Hyd/ Jamshoro with the duration of one year from 01-03-2009 to 28-02-2010, two hundred cases of diabetic nephropathy were included in this study after diagnosed cases of diabetes mellitus with nephropathy presenting with symptoms and signs of hypoglycemia. All cases of alcoholics, with severe malnutrition and starvation, Co morbidities like Chronic liver disease, Tuberculosis, Malignancy, patients with renal diseases without diabetes and hypoglycemia due to other causes were excluded from the study. Known diabetic patients with nephropathy in the emergency department and medical units. Liaquat university Hospital Hyd/ Jamshoro, who presented with common symptoms and signs of hypoglycemia as mentioned in proforma annexed were included in this study. Their blood sugar level was checked if below 50-45mg/dl were labeled as hypoglycemia. Hypoglycemic patients were treated first. A detailed history was taken either from patient himself/herself or a family member, questions were specifically asked about duration of the diabetes, type of anti diabetic drugs patient was taking, for how long patient is taking these drugs, also questions regarding any acute or chronic illness were asked. After that detailed examination was carried out, meanwhile patient's urine for detailed report and blood for measurement of serum urea and creatinine were sent to laboratory. Previous and current investigations were reviewed, ultrasound for kidneys was done, 24 hour urinary proteins were advised and method for collecting the urine was explained to the patient or attendant where necessary, this test was not repeated if done in last 6 months. Investigations were done in the emergency and main laboratory of LUH Hyd; investigations done in other recognized laboratories were also accepted.

DATA ANALYSIS PROCEDURE

The data was entered and analyze into Statistical packages for social science (SPSS version 10.0). Frequency and percentage were computed for categorical variable like sex, type of diabetes, clinical presentation, hypoglycemic and non hypoglycemic patients.

Mean and standard deviation were computed for quantitative variables like age, duration of disease, weight, systolic and diastolic blood pressure, pulse and respiratory rate.

Mann Whitney U test was applied to compare significant difference between hypoglycemic

and non hypoglycemic patients for age, weight, systolic and diastolic blood pressure, pulse and respiratory rate.

Chi-square test was also applied to compare proportion difference between hypoglycemic and non hypoglycemic patients for clinical presentation. $P \leq 0.05$ was considered level of significant.

RESULTS

A total of 200 diagnosed cases of diabetes mellitus with nephropathy presenting with symptoms and sign of hypoglycemia were included in this study.

The average age of the patients was 61.22 ± 10.21 years (95%CI; 59.80 to 62.64). Age distribution of patients is presented in table 1. Most of the patients were belonged 60 to 79 years of age.

Out of 200 patients, 102(51%) were males and 98(49%) were females with 1.04: 1 male to female ratio as shown in figure 2. Twenty one (10.5%) patients had type I diabetes and 179(89.5%) had type II diabetes patients as shown in table I.

Frequency of hypoglycemia in patients with diabetic nephropathy, Out of 200 patients, 23(11.5%) patients had observed hypoglycemia (blood sugar < 45-50mg/dl) while 177(88.5%) were non- hypoglycemic patients. Frequency of hypoglycemia in patients with diabetic nephropathy according to gender was shown in table I.

Clinical presentation of the patients is presented in table II. Tremors was the most common presentation that was observed in 72% patients follow by dizziness 71%, palpitation was observed in 55%, sweating 49%, confusion 42%, slurred speech 23%, intense hunger 10% and loss of conscious was observed in 4% patients.

Comparison of median age, duration of diabetes, weight, systolic and diastolic blood pressure, pulse and respiratory rate are presented in table III. Duration of diabetes and diastolic blood pressure were not statistically significant difference between hypoglycemic and non hypoglycemic patients while median of age, weight, pulse, SBP and respiratory significant in hypoglycemic patients than non hypoglycemic patients.

Characteristics	No. of patients	%
Gender		
Male	102	51.0%
Female	98	49.%
Age groups		
< 50	22	11.0%
50 – 59	34	17.0%
60 – 69	86	43.0%
70 – 79	58	29.0%
Type I and type II diabetes patients		
TYPE I	21	10.5%
TYPE II	179	89.5%
Hypoglycemic	23	11.5%
Non-Hypoglycemic	177	88.5%

Table-I. Base line characteristics of the patients (n=200)

Characteristics	No. of patients	%	
Clinical Presentation	**Hypoglycemic patients (n=23)**	**Non-hypoglycemic patients (n=177)**	**P- value**
Sweating	23(100%)	75(42.2%)	0.0005*
Palpitations	17(73.9%)	93(52.5%)	0.05*
Dizziness	13(56.5%)	129(72.9%)	0.104
Confusion	17(73.9%)	67(37.9%)	0.001*
Tremors	21(91.3%)	123(69.5%)	0.028*
Intense hunger	4(17.4%)	16(9%)	0.209
Slurred Speech	8(34.8%)	38(21.5%)	0.153
Loss of conscious	6(26.1%)	2(1.1%)	0.0005*

Table-II. Clinical presentation of hypoglycemic and non-hypoglycemic patients
**Significant*

Variables	Hypoglycemic Patients (n=23)	Non-hypoglycemic Patients (n=177)	P-Values
	Median(IQR)	Median(IQR)	
Age (Years)	71(22)	61(12)	0.02*
Duration of diabetes (Years)	8(15)	11(9)	0.65
Weight (Kg)	70(15)	74(10)	0.027*
Pulse	105(10)	90(14)	0.001*
SBP, mmHg	158(12)	153(14)	0.026*
DBP, mmHg	81(8)	80(9)	0.218
Respiratory Rate	22(05)	17(6)	0.0001*

Table-III. Comparison of demographic and clinical features between hypoglycemic and non-hypoglycemic patients (n= 200)
Mann-Whitney U test applied

DISCUSSION

The aim of this study was to see the frequency of hypoglycemia in diabetic patients with nephropathy. As hypoglycemia is the major problem of the diabetic patients and it limits the strict glycemic control strategy in these patients, can cause permanent neurological deficit even death in 2-4% of patient in a year.[14]

In this study we selected 200 patients of type-1 and type-2 diabetes, who had developed nephropathy from both male and female gender, on the basis of common autonomic and neuroglycopenic symptoms. The inclusion criteria was diagnosed cases of diabetes with nephropathy presenting with common symptoms and signs of hypoglycemia either recently diagnosed with nephropathy or were on renal replacement therapy due to chronic renal failure or end stage renal disease. Excluded cases to make sure that no patient with renal disease other than diabetic nephropathy be included in this study.

Type-1 diabetics constituted 11% of total patients the ratio of type-1 and type-2 diabetes is almost the same as found in other studies around 10% in Pakistan as well as in rest of the world.[15,16] There was slight preponderance of male patients in diabetic with nephropathy; it could be because of, smoking and central obesity more common in male gender. Gross JL et al in their study had shown more prevalence of nephropathy in male gender.[17]

No study has been conducted on this topic either in Pakistan or internationally however, there are many studies that support our study.

A study innorthern Europe of unselected population with type-1 diabetes, conducted by tiebreak EWMT et al, incidence of severe hypoglycemia ranged from 1.0to 1.7 episodes per patient per year. The annualprevalence was between 30% and 40%[18], in our study, out of 23 hypoglycemic patients, 5(21.7%) were type 1 diabetics in which 1 was male and 4 were female further our patients were suffering from nephropathy and incidence of hypoglycemia is increased in these patients because drug excretion is decreased and gluconeogeneses by kidneys is also impaired in diabetic nephropathy depending on the stage of nephropathy.

A population survey conducted by Leese GP et al in a region of Scotland, in which all episodes of severe hypoglycemia that were attended by the emergency medical serviceswere identified over a 12-month period. A total of 244 episodes of severe hypoglycemia were recorded in 160 patients, comprising 69 people with type-1 diabetes, 66 type-2 diabetes treated with insulin, and 23 were managed with sulfonylurea. Age, duration, and socioeconomic status were identified as risk factors for severe hypoglycaemia.[19] In our study patients presented with longer duration of diabetes, mostly were type-2 and their socioeconomic condition was poor.

A retrospective Scottish survey in Edinburgh of

215 people withinsulin-treated type-2 diabetes observed that the frequency of hypoglycemia increased with duration of insulin therapy andof diabetes. The annual prevalence of severe hypoglycemia was 15% within overall incidence of 0.28 episodes per patient per year.[20]

Various studies have been conducted showing the frequency of hypoglycemia in diabetic patients taking oral anti diabetic drugs few are mentioned here.

Over 6 years of follow-up of patients with type-2 diabetes in the U.K. Prospective Diabetes Study (UKPDS), 2.4% of those using metformin, 3.3% of those using a sulfonylurea, and 11.2% of those using insulin reported major hypoglycaemia.[21]

In Diabetes Control and Complications Trial (DCCT 65% of the intensively treated patients with type-1 diabetes suffered severe hypoglycemia over 6.5 years of follow-up. Since the UKPDS involved newly diagnosed type-2 diabetes and the patients' glycemic control was not as strict as in the DCCT, the UKPDS data may well underestimate the frequency of hypoglycemia in type-2 diabetes.[22]

Another study conducted in England of 219 people with type-2 diabetestreated with sulfonylureas and/or metformin observed that 20%of those taking sulfonylureas had experienced symptoms of hypoglycemia in the preceding 6 months.[23] In our study patients were using insulin or oral hypoglycemic agents but compliance was the major problem in almost all these patients.

It has been discussed that diabetic nephropathy is the major cause of renal failure and terminated point of diseased of the kidneys, diabetic nephropathy affects 20% to 40% of both type-1 and Type-2 diabetics. ESRD develops in 50% of type-1 diabeticindividuals with overt nephropathy within 10 years and in >75%by 20 years[6], according to Rossing K et al Approximately 3% of newly diagnosed type-2 diabetic patients have overt nephropathy.[24] In our study all patients selected were suffering from diabetic nephropathy, they may be suffering from incipient nephropathy to end stage renal disease.

Earle KK et al had described in their study that about 30-40% of patients currently admitted for renal replacement therapy suffer from diabetic nephropathy. The occurrence of nephropathy in type-2 diabetes is 10 times more frequent than type-1 diabetes. The incidence is higher among subjects of Indo-Asian & African-Caribbean origin as compared to Caucasians. The rate of decline of renal functions is also accelerated in Indo-Asian subjects.[25] In our study the ratio of type-1 and type-2 diabetic patients suffering from nephropathy is also comparable to other studies i.e., type-1 diabetic with nephropathy were 10.5% and type-89.5%.

As the metabolism of insulin or oral hypoglycemic drugs is impaired in renal failure, causing hypoglycemic attacks in these patients.[13,26] A study conducted in Pakistan by Rashid K et al found a reduction of 28.2- 60% in insulin requirement in type-1 diabetics and about 35.2% patients of type-2 diabetes did not require any insulin for their diabetes control after development of renal failure due to diabetic nephropathy.[27]

A population-basedstudy in Germany examined the incidence of hypoglycemia in patients with type-2 diabetes who had attended a hospital emergency departmentover a 4-year period a total of 148 type-2 diabetic patients attended the emergency department due to severe hypoglycemia. The annual rate of severe hypoglycemia was 1.5 episodes per 100 patients in insulin-treated type-2 diabetics compared with a rate of 0.4 episodes per 100 patients for the overall group of type-2 diabetic patients. Irrespective of the treatment, the most frequent contributing factors for hypoglycemia in type-2 diabetic patients were advanced age (76 +/- 12 years) and renal impairment in 54% of patients (80 out of 148 patients).[28]

In our study 80% of patients were above 50 years of age and all patients had nephropathy ranging from incipient nephropathy to ESRD.

McAulay V et al found that it was difficult to derive equivalent figures of hypoglycemia for people withtype-2 diabetes because of the heterogeneity of this disorder.Most people with type-2 diabetes were middle aged or elderly; accurate measures of the frequency of hypoglycemia were probably underestimated in this age group, the manifestations of hypoglycemia in elderly people may be mistaken for otherconditions, such as transient ischemic attacks or vasovagal episodes. Many elderly people with type-2 diabetes possess littleknowledge of the symptoms and treatment of hypoglycaemia.[29]

We also faced the same problem most of our patients were elderly, type-2 diabetics and had little knowledge about their disease.

It is clear from above discussion that there was a great difference of frequency of hypoglycemia between various studies.

In this study we found that, on the basis of common symptoms 12% had actual hypoglycemia, 88% of patients had normal or above normal blood sugar level. Most of the patients in our study were middle and old age and symptoms mimicking hypoglycemia were common in this age group. After brief history and examination it was found that most of the patients were not in regular follow-up, from a long time they were on the same treatment and same dose as prescribed by a health care provider. Drug compliance was a major problem in these patients. Some patients were trying to maintain the strict glycemic control without giving importance to their renal function.

Though a wide variation of hypoglycemic episodes had been seen in diabetic patients in various studies worldwide due to multiple factors we also faced the same problems few are mentioned here.

In this study diabetic patients with nephropathy were selected on the basis of symptoms and signs of hypoglycemia no matter in which stage of nephropathy or renal failure they were, or were they trying to achieve strict glycemic control or not. This study cannot be accurate because most patients were elderly, they may have been suffering nocturnal attacks of hypoglycemia or due to long standing diabetes and repeated episodes of hypoglycemia they may have developed hypoglycemic unawareness, further we have not selected the particular type of diabetes or study has not been conducted on the basis of duration of diabetes or on the basis of particular class of drug patients were taking. Neither we selected particular number of patients to follow them and record episodes of hypoglycemia that may require years of follow-up and was not possible in our setting. Many diabetic patients come to know the symptoms of hypoglycemia and are treated by them, family members or by health care providers near to them at that time and had been missed in our study. In our study we selected patients fulfilling our inclusion criteria no matter from where they are coming. So further studies are required in this field particularly for each variable separately.

CONCLUSION

This study concluded that diabetic patients with nephropathy are at risk of hypoglycemia, they may even develop ESRD and drug metabolism is impaired in renal failure, so these patients should be in proper follow-up and their treatment regimens should be reviewed and changed accordingly. Health care providers should pay attention not only to diabetes but also its complications and suggest treatment according to the stage of the disease and its complications, further patients should be educated and guided accordingly.

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"Nothing in the world is more dangerous than sincere ignorance and conscientious stupidity."

Martin Luther King Jr. (1929-1968)

AUTHORSHIP AND CONTRIBUTION DECLARATION

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