INSULIN REQUIREMENT IN DIABETIC PATIENTS WITH CHRONIC RENAL FAILURE DUE TO DIABETIC NEPHROPATHY (DN)

KAMRAN RASHID, KHALIL UR REHMAN, M. SAEED ANWER
AAEISHA QURESHI AND R. A. BASHARAT
Departments of Medicine and Pathology, Postgraduate Medical Institute/ Lahore General Hospital, King Edward Medical College and Department of Population Welfare, Lahore

This study was performed in the Department of Medicine, Postgraduate Medical Institute and Lahore General Hospital, Lahore. One hundred patients of type 1 and type 2 diabetes with diabetic nephropathy induced chronic renal failure, of either sex; the ages above 18 years were included in the study. Patients, recruited, were investigated to rule out any other cause of renal failure. Data was collected on a questionnaire regarding duration of diabetes, previous diabetic treatment and compliance. Patients were put on insulin and their daily blood glucose charts were maintained. When the patients achieved optimal glycaemic control, total amount of insulin per day was recorded. This study included a total of 100 diabetics, 12 (7 men, 5 women) had type 1 and 88 (41 men, 47 women) had type 2 disease. Duration of diabetes was higher in type 1 (15.6±3.2 years) than in type 2 diabetes (9.7±5.0 years). All patients with type 1 diabetes required insulin but there was reduction of 28.2%-60.0 % as compared to maximum units taken prior to renal impairment. About 35.2% patients of type 2 diabetes did not require any insulin. Mean insulin requirement was lower in type 2 diabetics (14.8±14.6 units/day) than in type 1 diabetics (34.3±9.9 units/day). The Pearson correlation (2-tailed) between serum creatinine and 24 hour insulin requirement was significant (P=0.01). The purpose of this study was to find out the requirement of insulin for optimal glycaemic control in diabetics with impaired renal function due to diabetic nephropathy. It was concluded that the patients with impaired renal function due to DN had lower requirement of insulin than before the development of DN. Type 1 diabetic patients had significant reduction in insulin compared to the requirement prior to DN. Some type 2 diabetic patients did not require any treatment.

***Key Words**: Insulin requirement, Diabetic nephropathy, chronic renal failure, Type 1 diabetes, Type 2 diabetes.*

INTRODUCTION

Insulin plays a key role in the homeostasis of glucose. Exogenous insulin administration is used to control diabetes mellitus (DM)[1]. During pre-insulin era; no effective treatment was available for this malady. Majority of the patients with chronic renal failure (CRF) due to diabetic nephropathy (DN) are controlled on insulin[1]. Clinically DN is defined as the presence of persistent proteinuria (0.5g/day) in a diabetic patient with retinopathy, elevated blood pressure and declining glomerular filtration rate (GFR) in the absence of urinary tract infections (UTI), other renal diseases or cardiac failure[2]. It affects 20 to 30 percent of type 1 and type 2 diabetic patients[3,4].

Raised blood glucose level and related microvascular disease is associated with progressive damage to kidneys. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (>30 mg/day or 20 μg/min) of albumin in the urine, referred to as microalbuminuria, and patients with micro-albuminuria are referred to as having incipient nephropathy.[5] Without specific interventions, ~80% of diabetics who develop sustained microabluminuria have their urinary albumin excretion increase at a rate of ~10-20% per year to the stage of overt nephropathy or clinical albuminuria (>300 mg/day or >200 μg/min) over a period of 10-15 years[6].

Without specific interventions, GFR gradually falls over a period of several years. However, there

is little change in metabolic clearance rate of insulin in renal disease until there is substantial reduction in GFR (i.e. < 20ml/min). The kidneys metabolize most of the oral hypoglycaemic agents and they tend to accumulate during renal failure. This causes the risk of hypoglycaemia and toxicity. Many specialist centers prefer to transfer all patients receiving oral hypoglycaemic agents to insulin when serum creatinine concentration reaches 2.4 mg/dl[7]. As the renal failure progresses, insulin clearance and degradation by the kidneys decreases. The insulin sensitivity and insulin secretion is also decreased[8]. Insulin treatment in the diabetic patients with impaired renal function due to DN is characterized by two features:

- Increased risk of hypoglycaemic episodes.
- Poor metabolic control as compared to diabetics with normal renal functions.

A recent study conducted in type 1 diabetics with DN has shown increased insulin levels and decreased insulin clearance by 30% to 40%. It showed mild reduction in insulin requirements[9]. Hardly any such study has been conducted in Pakistan so far. In our clinical experience diabetic patients suffering from CRF require less insulin for optimal glycaemic control. This reduction is unpredictable. If the insulin dosage is not regulated properly, this can lead to hypoglycaemic episodes or poor metabolic control. This cross-sectional study was conducted to find out the requirement of insulin in patients with impaired renal function due to DN.

PATIENTS AND METHODS

This cross-sectional descriptive study examined one hundred diabetics (12 type 1, 88 type 2) with DN seen consecutively at Lahore General Hospital, Lahore from Aug 2002 to Nov 2003. All Patients had DN induced CRF and belonged to both sexes and had ages above 18 years. Type 1 diabetics included thin and lean patients who required insulin for glycaemic control since the start of their treatment. On the other hand type 2 diabetics were taken as those patients who initially had optimal glycaemic control on oral hypoglycaemic agents later on they may have required insulin. CRF due to DN was diagnosed on the basis of serum creatinine ≥ 2.4 mg/dl and proteinuria > 500 mg/day. Patients with type 1 DM of less than 5 years duration[10], patients who suffered from high grade fever resulting in increased requirement of insulin, dehydration, connective tissue diseases, malignancies, UTI, haematuria or other causes of renal failure were excluded from the study.

In emergency and outpatient departments, after taking an informed consent from diabetic patients; their brief history, clinical examination and review of any previous or current investigations was carried out. Patients with a provisional diagnosis of DN were admitted to the ward. In the ward detailed history and clinical examination were performed. Questions were specifically asked about the duration of diabetes, presence of fever any other acute or chronic illness and urinary complaints like dysuria, haematuria and pyuria. Clinical examination including fundoscopy was carried out. Signs of diabetic retinopathy were looked for. The presence of the background diabetic retinopathy was considered sufficient for this diagnosis.

Those patients in whom no exclusion criteria were found on the history, clinical examination, review of investigations and fundoscopy, were further investigated through urine routine examination, white cell count and ultrasonography of renal system. After inclusion and exclusion criteria were satisfied, patients were enrolled for the study. Those patients who were taking oral hypoglycaemic agents were put on insulin. Insulin was started from low dose and gradually increased for optimal glycaemic control. Regular, NPH or pre-mixed NPH and regular insulin in the ratio of 70% and 30% respectively were used as required in a particular case. Injections were given on abdomen.

The data was collected on a proforma, which included a questionnaire and the laboratory results as well as the units of insulin, required daily to achieve optimal glycaemic control. Patients having diabetes for less than six months were taken as newly diagnosed and those having diabetes for 6-12 months were rounded up to one year. Previous treatment taken for diabetes was noted. The maximum units of insulin taken previously by type 1 diabetics were also asked provided that patient did not suffer from any other ailment (stress, trauma, surgery or high grade fever) during that period. Compliance of the past treatment was noted. Compliance was defined as the extent of correspondence between the patient's actual dosing history and the prescribed regimen[11]. Blood glucose was estimated in the pathology laboratory or using a glucometer (Meditest).

Blood glucose was performed four times daily. These were fasting, pre-lunch, pre-dinner, and at bedtime. When required blood glucose at any other time was also checked. Insulin doses were increased or decreased for optimal glycaemic control. When the control was achieved for at least two days, the mean total dose of insulin required

per day was calculated and noted on the questionnaire. Optimal glycaemic control was defined as fasting plasma glucose <110 mg/dl and random plasma glucose < 180 mg/dl.

The study data was entered and analyzed using SPSS v 10.1. The data was presented as means and percentages. Two means were compared using a t- test. The level of significance was at 0.05. Pearson correlation (2-tailed) was used to find correlation between serum creatinine and total units of insulin required. A scatter graph was also made to describe daily insulin requirement according to serum creatinine.

RESULTS

A total number of 100 diabetics, 12 with type 1 (7 men, 5 women), and 88 with type 2 disease (41 men, 47 women) were examined in this cross-sectional study. All the patients suffered from CRF due to DN. Only those diabetics were enrolled in the study who had nephropathy accompanied by diabetic retinopathy. Clinical and laboratory characteristics of study population are described in Table 1. The mean age in patients with type 2 DM was higher than those with type 1 disease ($p< 0.05$), whereas duration of disease was longer in type 1 diabetics than type 2 diabetics ($p< 0.05$). In type 2 DM the mean duration was less than 10 years and no significant difference of duration on the basis of gender was observed. Four patients were newly diagnosed and 14 patients had disease for more than 15 years.

Majority (n=31) of the diabetics had serum creatinine between 2.4 - 4.5 mg/dl (Fig. 1). The serum creatinine was higher in type 2 diabetics than type 1 diabetics ($p< 0.05$). Mean insulin requirement was significantly lower in type 2 DM than type 1 DM. Many patients with type 2 disease (35.2%) did not require any insulin for optimal glycaemic control. All type 1 diabetics required insulin; however there was a dose reduction in the range of 28.2%-60.0% compared to the maximum units of insulin taken previously in the absence of any other ailment (Table 2). When considered separately for both type 1 and type 2, men required more insulin than women (21.0±17.2 units vs. 13.6±13.0 units). A significant Pearson correlation between serum creatinine and total units of insulin required per day was found ($p = 0.01$) (Fig. 2). With increasing serum creatinine levels, patients required progressively less insulin. Mean 24 hour urinary protein was 1452.5 mg/dl (range 712-4788 mg/dl).

The compliance was poor in all the patients with type 2 diabetes. Only 3 (25%) patients with type 1 diabetes had adequate compliance. Most of the patients were unable to remember the names of oral hypoglycaemic agents they had taken previously.

Table 1: *Clinical and laboratory characteristics of diabetic population.*

Characteristic	Type 1 Diabetes (n=12)	Type 2 Diabetes (n=88)	All patients (n=100)
Mean age (years)	34.8±5.3	55.8±7.2	53.3±9.8
Sex (men, women)	7,5	41,47	48,52
Duration of diabetes (years)	15.6±3.2	9.7±5.0	10.5±5.2
Serum creatinine (mg/dl)	3.3±1.4	4.1±1.8	4.0±1.8
Insulin requirement (Units/day)	34.3±9.9	14.8±14.6	17.2±15.5

Table 2: *Units of insulin required before and after diabetic nephropathy in Type 1 diabetes.*

No	Gender	Age (years)	Serum Creatinine (mg/dl)	Insulin Required (U/ d)	Previous Insulin taken (U/d)	Percent reduction
1	Male	30	6.0	22	42	47.6
2	Male	36	2.9	32	64	50.0
3	Male	35	2.6	46	64	28.2
4	Female	34	6.4	16	40	60.0
5	Male	29	2.4	34	60	43.3
6	Female	42	2.4	52	84	38.1
7	Male	27	2.4	42	72	41.7
8	Male	35	2.5	36	58	37.9
9	Female	45	3.2	30	72	58.4
10	Female	37	3.0	30	52	42.3
11	Female	30	2.8	40	62	35.5
12	Male	38	2.6	32	52	38.5

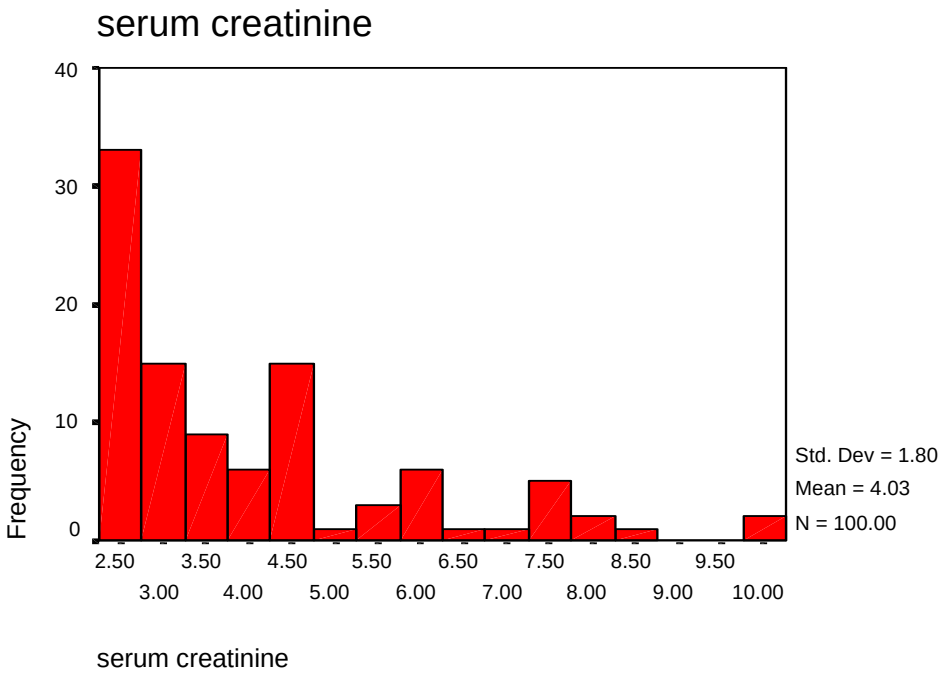

Fig 1: Frequency distribution of serum creatinine level (mg/dl) in study population.

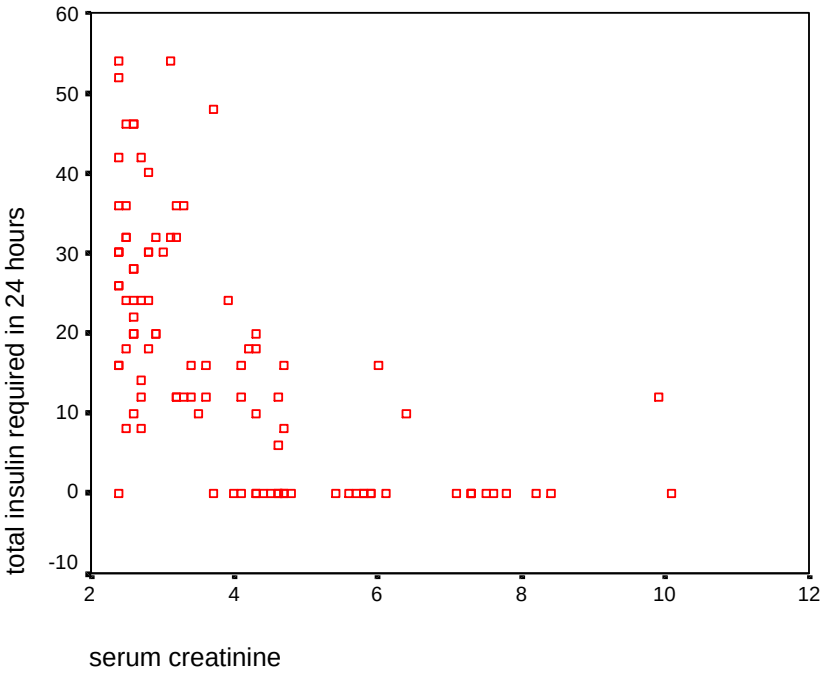

Fig 2: Pearson correlation of serum creatinine (mg/dl) with insulin requirement (units).

DISCUSSION

This study included sufficient number of male and female patients of both type 1 and type 2 diabetes. The inclusion criteria were designed to include only those patients who have developed stage 5 nephropathy i.e. CRF. This was because these were the patients who required progressively less insulin or even cessation of therapy in our clinical observations. The exclusion criteria were designed to make sure that no patient with suspicion of renal disease other than DN be included in our study. The patients were asked about the previous treatment they had taken for glycaemic control. Type 1 diabetic patients were asked about the maximum insulin units they had taken prior to development of DN in the absence of any other disease like infection etc. It was then compared with the current requirement of insulin after the development of impaired renal function. These results clearly showed a reduction in the requirement ranging from 28.2% to 60.0%. These results could be influenced by the memory bias due to the long duration of time for which patients had been suffering from diabetes and insulin.

Type 2 diabetic patients required lesser amount of insulin for glycaemic control as compared to type 1 diabetics. Thirty-one patients out of 88 (35.2%) did not require any insulin. Many patients required only a single daily injection of insulin. This indirectly showed the increased duration of action of insulin in these patients. It can be explained on the basis of the fact that there is 30% to 40% reduction in insulin clearance in patients with DN as compared to those without nephropathy and decrease in the renal gluconeogenesis in these patients that otherwise is increased in both type 1 and type 2 diabetic patients. This fact is proved by increased insulin levels found in patients with nephropathy[9]. The patients who did not require any insulin may have sufficient endogenous insulin produced for glycaemic control. Anorexia and weight loss associated with the CRF may also be a factor. Type 1 patients required larger doses of insulin than type 2 patients. This is because type 1 patients did not have any endogenous insulin production. Majority of the patients who presented had serum creatinine between 2.4-4.5 mg/dl. This could be because of the fact that patients with higher serum creatinine are usually referred to specialized nephrology units for possible dialysis by general practitioners and other peripheral hospitals.

There was significant correlation between serum creatinine and the total units of insulin required. With increasing serum creatinine levels patients required less insulin. This was found contrary to the results of another recently conducted study by Rave K et al[9]. This study found

only mild reduction in insulin requirements in diabetic patients with impaired renal functions as compared to diabetic controls with normal renal functions. However the selection criteria of two studies were much different as it included patients with mild renal function impairment. No other study similar to the present study could be found from Pakistan or international literature for comparison. There is a study on insulin requirements in type 1 diabetic patients developing acute renal failure conducted by Weinranch and associates[8]. This study has shown decreased insulin requirement during the period of acute renal failure. The patients reverted back to their original requirement as their renal functions improved. Various textbooks and authors have mentioned about the reduction in the requirement[7,12].

One of the limitations of the study was that GFR was not done. However the GFR is more important to assess the renal impairment when the serum creatinine is still within normal limits or only mildly increased which was not the case in our study where patients had already developed advanced renal failure. Serum creatinine starts rising when GFR has reduced to less than 70%[7].

Type 1 diabetics constituted 12% of total patients which is the same as found by other studies[13]. In type 1 diabetes number of men was slightly more than women. Studies have shown male gender as risk factor for DN[14]. The men had lesser average age, shorter duration since onset of diabetes and required more units of insulin as compared to the female patients. This could be explained by increased prevalence of smoking in males. Poor compliance noted in all the type 2 and majority of type 1 diabetics is the reason for early development and rapid progression of DN and other diabetes related complications in our patients. Poor compliance is due to lack of knowledge about their disease in diabetic patients[15].

CONCLUSSION

This study concluded patients with CRF due to DN require less insulin for their glycaemic control. So decrease in the requirement should be anticipated as the diabetic patients develop renal failure. Many type 2 diabetic patients will not need any treatment for optimal glycaemic control. Education is needed for patients as well as the health care providers regarding the diabetes to improve the compliance and counter its complications.

REFERENCES

1. Mcfarlane IA, Bliss M, Jackson JGL, Williams G. The history of diabetes mellitus. In: Pickup J, Williams G eds. Textbook of Diabetes 2nd ed. Oxford: Blackwell Science, 1997; 1: 1-19.
2. Barnes JD, Pinto JR, Viberti GC. The patient with diabetes mellitus. In: Davidson AM, Cameron JS, Grunfeld JP, Kerr DNS, Ritz E, Winerals CG eds. Oxford Textbook of Clinical Nephrology. London: Oxford Medical Publications, 1997: 723-57.
3. Ritz E, Orth SR. Nephropathy in patients with type 2 diabetes mellitus. N Engl J Med 1999; 341: 1127–33.
4. Augustine J, Donald G. Diabetic nephropathy [online article], The Cleveland Clinic, Department of Nephrology and Hypertension, The Cleveland Health Foundation, United States 2003.
5. Diabetic Nephropathy (online article) American Diabetic Association: Clinical Practice Recommendations 2001.
6. Pharmacology of diabetes mellitus: Insulin treatment (2004) [online article], Gopi Memorial Hospital, Tamil Nadu, India.
7. Grenfell A. Clinical management of diabetic nephropathy. In: Pickup JC, Williams G eds. Textbook of Diabetes 2nd ed. Oxford. Blackwell Science 1997; 54:1-15.
8. Weinranch LA, Healy RW, Leland OS. Decreased insulin requirement in acute renal failure in diabetic nephropathy. Arch Intern Med 1978; 138: 399-405.
9. Rave K, Heise T, Pfiitzner A, Heinmann L, Sawicki PT. Impact of diabetic nephropathy on the pharmacodynamic and pharmacokinetic properties of insulin in type 1 diabetic patients. Diabetes Care 2001; 24: 886-90.
10. Collaborative Study Group, United Kingdom. Microalbuminuria in type 1 (insulin-dependent) diabetic patients: prevalence and clinical characteristics. Diabetes Care 1992; 15: 495-501.
11. Yusuf M, Ali M, Bano I. Compliance of drug therapy and reasons of non-compliance among hypertensive patients: Experience at Lahore, General Hospital Lahore. Pakistan J Med Sci 2000; 16: 65-8.
12. Barnes JD, Pinto JR, Viberti GC. The patient with diabetes mellitus. In: Davison AM, Cameron JS, Grunfeld JP, Kerr DNS, Ritz E, Winerals CG eds. Oxford Textbook of Clinical Nephrology. London: Oxford Medical Publications, 1997: 723-57.
13. Rehman AU, Khan JA, Abaidullah S, Zaheer J, Hassan M. Characteristics of diabetic patients and patterns of diabetic complications. Ann King Edward Med Coll 2000; 2: 196-9.
14. Jackbson P, Rossing K, Tarrow L, et al. Progression of diabetic nephropathy in normotensive type 1 diabetic patients. Kidney Int 1999; 71: S1001-5.
15. Jabbar A, Contractor Z, Ebrahim MA, Mahmood K. Standard of knowledge about their disease among patients with diabetes in Karachi, Pakistan. J Pak Med Assoc 2001; 51: 216-8.