Current Trends in Endocrinology
Vol. 7, 2014

Original Communication

Glycemic control with intensive insulin treatment fundamental to renal preservation in diabetes

Anil K. Mandal[1,*], Linda M. Hiebert[2] and Harry Khamis[3]

[1]Mandal Diabetes Research Foundation and Department of Medicine, University of Florida, Gainesville, Florida, USA. [2]Department of Veterinary Biomedical Sciences, University of Saskatchewan, Saskatoon, Canada. [3]Statistical Consulting Center, Wright State University, Dayton, Ohio, USA

ABSTRACT

Diabetes is the most common cause of end stage renal disease (ESRD). Previous studies imply that angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blocking (ARB) drugs contribute to prevalence of ESRD in diabetes. This study investigates renal preservation in diabetes by intensive insulin therapy. 46 adult diabetes patients, 28 females and 18 males were studied for mean 14.2 months (1.5-115 months). Diabetes was diagnosed by 2-h postprandial glucose of ≥ 200 mg/dL (11.1 mmol/L) and treated by Glargine or detemir insulin administered after breakfast and dinner, with regular insulin by finger-stick glucose 2-h post-meal and bedtime. Blood pressure (BP) was controlled with anti-hypertensive therapy excluding ACEI/ARB drugs. Glucose, serum creatinine (Scr), estimated glomerular filtration rate (eGFR), and glycosylated hemoglobin (HbA_1c) at first and last visits were obtained. BP was recorded in both visits. Results were compared between first and last visits. A paired two-tailed test $P < 0.05$ was significant. Patients were divided by 2hPP glucose of < or > 11.1 mmol/L. Glucose at last visit was significantly lower (8.4 ± 0.6 mmol/L) than first visit (10.3 ± 0.7 mmol/L) in all patients group associated with significantly reduced Scr in last visit (100.3 ± 5.2 µmol/L) compared to first visit (110.9 ± 7.8 µmol/L). No change in eGFR was noted between first and last visits. Significant reduction of HbA_1c (9.14 ± 0.52 v. 7.60 ± 0.45%, $p < 0.0148$) was found in less than 11.1 mmol/L group. BPs were normal (< 140/80 mmHg) in both visits in all groups. The paradigm of therapy presented in this study is proven effective in renal preservation in diabetes.

KEYWORDS: diabetes mellitus, ACEI/ARB, glargine insulin, renal preservation, blood pressure

1. INTRODUCTION

Diabetic nephropathy is the most common cause of end stage renal disease (ESRD) worldwide [1-3]. A proportion of the patients with diabetes mellitus (DM) also have uncontrolled hypertension. In developed countries, ESRD is a major cost driver for health care systems, with annual growth of dialysis programs ranging between 6% and 12% over the past two decades. These costs continue to grow, particularly in developing countries [3]. Treatment of ESRD with dialysis in the USA alone costs Medicare and other insurance companies 50 billion dollars annually as of 2007 [4], yet with poor quality of life. Our previous studies indicate that high incidence of ESRD in diabetes is mainly related to overenthusiastic use of renin-angiotensin inhibitor drugs and little attention to glycemic control [5-6].

We have asked an important question if prevention of ESRD, hence life without dialysis treatment, is

*Corresponding author: Anil K. Mandal,
Medical Specialists of North East Florida,
665 State Road 207, Suite 102, Saint Augustine,
Florida 32084, USA.
amandal@med-spec.com

attainable by adequate glycemic control with intensive insulin treatment in diabetes.

Many studies in the past have documented the benefits of glucose control in prevention of microvascular and macrovascular complications in diabetes [7-10]. However, no study has systematically examined if intensive glycemic control reduces the risk of progression of diabetes related chronic kidney disease (CKD) into ESRD. More importantly, there is little evidence to indicate that control of 2-hour postprandial (2hPP) hyperglycemia is effective in reducing the risk of diabetes-related ESRD.

Most recently, we have published our data from a study of 56 adult diabetics treated with intensive insulin therapy showing that renal function change is insignificant when 2hPP glucose is maintained below 11.1 mmol/L. We have innovated the factor of dglucose (2hPP – fasting glucose) and have shown that dglucose below 5.5 mmol/L is a stronger predictor of renal protection than 2hPP glucose [11].

The current work is intended to test our hypothesis that renal preservation is attainable by glycemic control with intensive insulin treatment and adequate blood pressure control with agents other than renin-angiotensin inhibitor drugs. Data are scarce with regard to control of 2hPP hyperglycemia related to prevention of progression of CKD into ESRD. Thus the purpose of this work is to add that missing evidence.

2. MATERIALS AND METHODS

A total of 46 patients are included in this study. All patients included in this study are part of routine office visits with the first author. Most patients were referred by primary care physicians for diabetes, hypertension and decreased kidney function. A few patients were self-referrals because of uncontrolled diabetes. Prior to referral, most patients were treated with oral hypoglycemic agents consisting of metformin, glyburide, glimepiride, sitagliptin (Januvia®) or a combination of these four drugs. A few patients were treated with rosiglitazone or pioglitazone alone. A few patients were receiving additional low dose of insulin Glargine or insulin Detemir at bedtime. Diagnosis of type 1 or type 2 diabetes is not used by the investigators for the sake of brevity [11]. On the other hand, we feel comfortable to use the definition of diabetes by the National Diabetes Data Group (NDDG), that an elevated 1-hour post challenge glucose value (≥ 11.1 mmol/L) in addition to an elevated 2-hour value be required for diagnosis of diabetes [12]. We have decided to use only the 2-hour value for the sake of convenience of the patients.

At the initial office visit, all medications were thoroughly reviewed to determine if any patient was taking hydrochlorothiazide (HCTZ) or chlorthalidone for hypertension. These thiazide diuretics produce hyperglycemia, mimicking diabetes or aggravate hyperglycemia in diabetes. Similarly, full attention is paid on whether the patients were treated with angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) to control hypertension and provide renal protection in diabetes. In most patients with decreased kidney function, ACEI and/or ARB were already discontinued by the primary care physician at the time of referral. Thus at the first visit, the following medicines were discontinued: HCTZ, chlorthalidone, and/or ACEI or ARB drugs. Oral hypoglycemic agents were continued through the next two or three visits. Notably, no patients in this study were treated with ACEI or ARB drugs to avert any adverse effects of these drugs on kidney function [5-6, 13].

Diabetes is redefined by laboratory study of fasting and 2hPP glucose and glycosylated hemoglobin (HbA_1c) levels. Patients were discretely instructed to go to the laboratory after overnight fasting, for a blood sample (fasting), basic metabolic panel (BMP) and HbA_1c, then to eat a breakfast containing foods equivalent to 70 grams of carbohydrate (most eat pancakes or sandwiches and juice) and return to the laboratory 2 hours later for another blood sampling (2hPP BMP). Patients were instructed to continue monitoring blood glucose levels at home, as before, and were scheduled for a return office visit one week later (First visit). BMP includes glucose, BUN, serum creatinine (Scr) estimated glomerular filtration rate (eGFR), Na^+, K^+, Cl^-, HCO_3^- and Ca^{++}. Diagnosis of established diabetes was made if 2hPPG is ≥ 11.1 mmol/L. Once the

diagnosis of established diabetes was made, they were started with insulin Glargine (Lantus®) typically 25 units after breakfast and 25 units after dinner (12 hours apart). Patients were instructed to obtain finger-stick glucose 2 hours after each meal and at bed time and to take regular insulin (Novolin® or Humulin®) according to standard or low sliding scale based on renal function. Thereafter, they were followed every four to six weeks with fasting and 2hPP BMP until 2hPP glucose levels were stabilized. Lantus dosage is adjusted upwards in subsequent visits to reduce 2hPPG < 11.1 mmol/L. When 2hPP glucose and renal function are stable, they are followed every eight to 12 weeks.

Staging of CKD was done as follows by eGFR [14].
Normal kidney function > 60 ml/min
CKD Stage 1 < 60 - ≥ 50 ml/min
CKD stage 2 < 50 - ≥ 40 ml/min
CKD stage 3 < 40 - > 30 ml/min
CKD stage 4 < 30 - ≥ 20 ml/min
CKD stage 5 < 20 - ≥ 10 ml/min
Stage 6 or ESRD < 10 ml/min

Patients with CKD stage 4 or higher are not included in this study.

Oral hypoglycemic agents are discontinued one at a time in each subsequent visit until all are discontinued. Thus all the patients in this study were solely treated with Glargine or detemir and regular insulin as stated before. Hypertension control was achieved with beta blocker or calcium channel blocker drugs or a combination of both, sympathetic inhibitor, vasodilator drugs and, in resistant patients, with low dose HCTZ or chlorthalidone recognizing the fact that the diuretic may increase glucose level and may decrease kidney function as already reported [15].

The 46 patients, 28 females and 18 males, were followed for an average period of 14.2 months ranging from 1.5 to 115 months. The mean age was 62.2 years (range 39-86 years). The following parameters were examined: systolic, diastolic and mean blood pressure; fasting glucose, 2hPP glucose, dglucose (2hPP-fasting); fasting serum creatinine (Scr), 2hPP Scr, dScr (2hPP-fasting); fasting eGFR, 2hPP eGFR and deGFR (2hPP-fasting) and HbA_1c. All data was obtained directly from laboratory tests except for mean blood pressure, dglucose, dScr, and deGFR which were calculated.

The values for each parameter were compared between the first and last visits using a paired two-tailed t-test. P values of < 0.05 were considered significant. Patients were divided on the basis of 2hPP glucose of < or > 11.1mmol/L.

3. RESULTS AND DISCUSSION

When patients were divided on the basis of 2hPP glucose of < or > 11.1 mmol/L, the number of patients that had 2hPP glucose < 11.1 mmol/L were 10 patients of 46 on the first visit and 15 patients of 46 on the last visit. Similarly, the number of patients that had 2hPP glucose > 11.1 mmol/L were 36 patients of 46 on the first visit and 31 patients of 46 on the last visit.

Table 1 shows the average fasting, 2hPP and d (2hPP – Fasting) glucose, Scr and eGFR at first and last visits in all patients and when 2hPP glucose is > or < 11.1 mmol/L at the first and last visits. As shown, there is no significant difference in all variables when values from the last visit are compared with the first, except for the fasting glucose in all patients. Fasting glucose 8.4 ± 0.6 mmol/L at the last visit is significantly lower than that of first visit (10.3 ± 0.7 mmol/L, $p < 0.0173$) (Table 1). Fasting glucose in the group of < 11.1 mmol/L was significantly lower (5.7 ± 0.36 mmol/L) at the last visit compared to that in the first visit (8.4 ± 1.2 mmol/L, $p < 0.0481$). Fasting Scr of 100.3 ± 5.2 mmol/L at the last visit was significantly lower than that of the first visit (110.9 ± 7.8 mmol/L) in all patients (Table 1). All averages for eGFR are greater when data from the last versus the first visits are compared, although the differences have not reached statistical significance. When staging of eGFR are plotted for all patients or patients with 2hPP glucose < or > 11.1 mmol/L there is little difference between the first and last visits but with a tendency towards improved kidney function (Figure 1). As shown in Table 2, average HbA_1c decreased in all categories when the last visit was compared with the first. However, in the category of < 11.1 mmol/L, HbA_1c decreased markedly (7.60 ± 0.45%) at the last visit compared to the first visit (9.14 ± 0.52%, $p < 0.0148$). Finally, as shown in Table 3,

Table 1. Average Fasting (F), 2 hour Postprandial (2hPP) and d (2hPP – Fasting) glucose, serum creatinine and eGFR at first and last visits in all patients and when 2hPP glucose is > or < 11.1 mmol/L.

	Glucose	First visit mmol/L	Last visit mmol/L	*P values	Scr	First visit µmol/L	Last visit µmol/L	*P values	eGFR	First visit mL/min	Last visit mL/min	*P values
All patients n = 46	F	10.3 ± 0.7	8.4 ± 0.6	0.017	F	110.9 ± 7.8	100.3 ± 5.2	0.013	F	56.4 ± 2.8	58.9 ± 3.2	0.202
	2hPP	15.2 ± 0.9	14.0 ± 0.8	0.281	2hPP	109.4 ± 6.1	106.0 ± 5.6	0.167	2hPP	54.7 ± 2.8	57.0 ± 3.3	0.257
	d	5.6 ± 0.6	5.6 ± 0.6	0.975	d	6.0 ± 1.3	5.8 ± 1.0	0.846	d	-1.61 ± 0.6	-1.94 ± 0.5	0.601
> 11.1 mmol/L n = 31	F	11.2 ± 0.8	9.6 ± 0.8	0.124	F	99.1 ± 7.4	95.8 ± 6.3	0.214	F	59.6 ± 3.4	60.5 ± 3.4	0.642
	2hPP	16.1±1.1	16.4 ± 0.7	0.839	2hPP	105.6 ± 7.9	101.2 ± 6.8	0.149	2hPP	57.1 ± 3.5	58.6 ± 3.6	0.494
	d	5.7 ± 0.7	6.7 ± 0.6	0.262	d	6.6 ± 1.6	5.4 ± 1.2	0.539	d	-2.4 ± 0.9	-1.9 ± 0.6	0.516
< 11.1 mmol/L n = 15	F	8.4 ± 1.2	5.7 ± 0.3	0.048	F	113.8 ± 8.8	111.0 ± 9.2	0.552	F	49.7 ± 3.1	56.2 ± 6.5	0.195
	2hPP	13.5 ± 1.6	8.9 ± 0.6	0.009	2hPP	118.5 ± 8.4	117.6 ± 9.7	0.823	2hPP	48.2 ± 3.2	53.3 ± 6.4	0.262
	d	5.3 ± 1.2	3.3 ± 0.5	0.073	d	4.8 ± 2.3	6.6 ± 2.1	0.438	d	-3.09 ± 0.09	-2.90 ± 1.10	0.270

Mean ± SEM.
*two-tailed paired t-test comparing differences between first and last visits for each parameter.

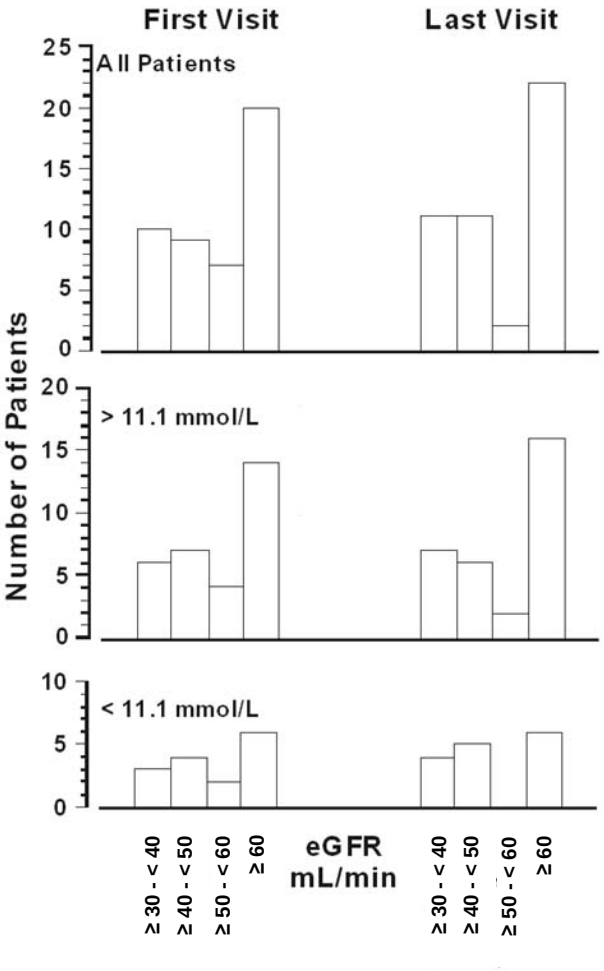

Figure 1. eGFR (mL/min). Number of patients at different stages of chronic kidney disease (CKD) as determined by the estimated glomerular filtration rate (eGFR) at first and last visits. In addition to the results for all 46 patients, results are divided for patients on the basis of 2hPP eGFR when 2hPP glucose is > or < 11.1 mmol/L. No difference is noted in eGFR between the two periods.

Table 2. Glycosylated Hemoglobin (HbA_1c) at first and last visits in all patients and when 2hPP Glucose is > or < 200 mg/dL.

	First visit	Last visit	P values
	HbA_1c %	HbA_1c %	
All patients	9.15 ± 0.32	8.61 ± 0.29	0.1785
> 11.1 mmol/L	9.16 ± 0.41	9.12 ± 0.33	0.9356
< 11.1 mmol/L	9.14 ± 0.52	7.60 ± 0.45	0.0148

average systolic, diastolic and mean pressures were less at the last visit in all groups. The diastolic blood pressure at last visit in the all patients group was significantly lower compared to that in the first visit (81.6 ± 1.9 vs 77.0 ± 1.5 mmHg; $p < .0297$).

Of major significance in this study, not reported before, is that renal function determined by serum creatinine and eGFR remained unchanged or has a tendency for improvement in a mean period of 14.2 months. This renal function pattern is seen equally in the group with 2hPP glucose < or > 11.1 mmol/L. Therefore, unchanged albeit slight improvement of renal function (decreased Scr) in the fasting period in all patients can be attributed to a combination of a) adequately defining established diabetes, b) new paradigm of therapy, namely use of Glargine or detemir twice daily rather than at bedtime only, and c) most importantly, complete exclusion of the use of ACEI and/or ARB drugs to control blood pressure and/or as renoprotective therapy in diabetes in our patients. Finally, as per mean eGFR (Table 1), all patients at most have CKD stage 1, but showed no progression in a period of 14.2 months. From Figure 1, it is evident that many patients in all groups have maintained near normal to normal renal function (eGFR $\geq$ 60 ml/min). Further a patient with longest follow up is presented here to demonstrate renal preservation with the paradigm of therapy which includes complete exclusion of the use of ACEI/ ARB drugs in this study (Figure 2).

In this study, we have defined established diabetes by 2hPP glucose > 11.1 mmol/L and examined longitudinally, renal function changes using Scr and eGFR data, obtained in a comfortable office setting. Data reveals that 2hPP glucose decreased to less than 11.1 mmol/L at the last visit in at least 15 of 46 patients (32.6%) by the paradigm of therapy consisting of Glargine or detemir insulin after breakfast and dinner (12 hours apart) and regular insulin as required by sliding scale determined by the patients themselves with finger-stick glucose 2h post meal and at bedtime. When relating glucose levels to outcome measures, such as progression of CKD to ESRD, it is important to obtain 2hPP glucose. It is already reported that patients with 2h post challenge glucose ≥ 11.1 mmol/L even when fasting glucose was unequivocally normal were at

Table 3. Average Systolic, Diastolic and Mean Blood Pressures at first and last visits in all patients and when 2hPP Glucose is > or < 11.1 mmol/L.

		First visit mmHg	Last visit mmHg	*P values First vs Last
All patients	Systolic	136.2 ± 3.3	133.6 ± 2.6	0.4777
	Diastolic	81.6 ± 1.9	77.0 ± 1.5	0.0297
	Mean	99.8 ± 2.0	77.0 ± 1.5	0.0806
> 11.1 mmol/L	Systolic	135.7 ± 4.2	133.1 ± 2.7	0.5495
	Diastolic	81.93 ± 2.3	77.6 ± 1.7	0.0795
	Mean	99.9 ± 2.6	96.1 ± 1.4	0.1383
< 11.1 mmol/L	Systolic	137.2 ± 5.4	134.6 ± 5.8	0.7154
	Diastolic	80.9 ± 3.5	75.7 ± 3.2	0.2233
	Mean	99.9 ± 3.4	95.3 ± 3.4	0.3644

*two-tailed paired t-test.

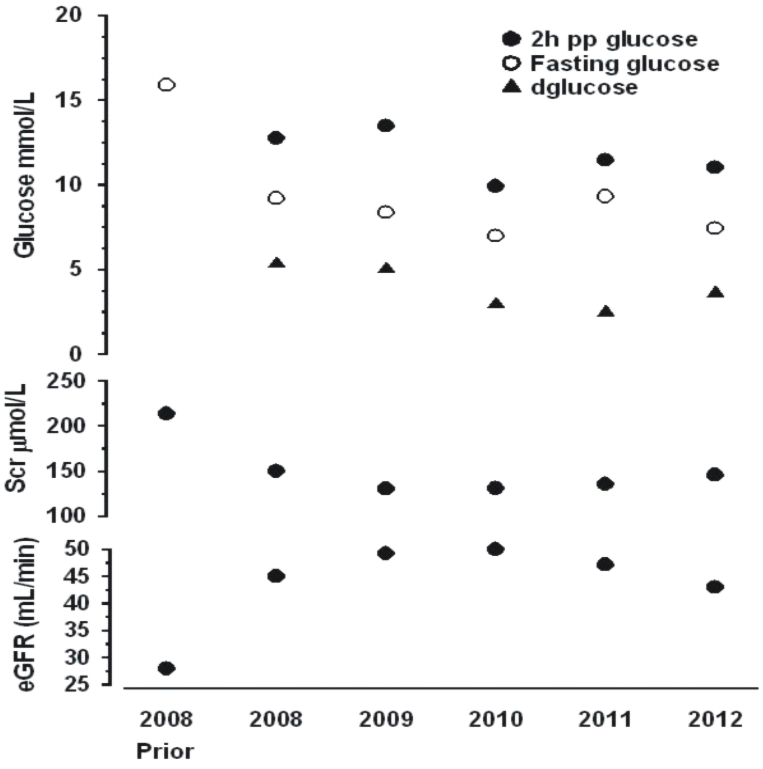

Figure 2. The data is obtained from a 75 year old white male who went to a urologist's office for difficulty in urination. At that visit diabetes was detected. He was treated with Glucotrol XL 10 mg PO daily, metformin 500 mg PO BID, enalapril 10 mg PO BID, furosemide 40 mg PO daily. He was admitted to a local hospital in February 2008 with acute renal failure. All previous medications were discontinued. Glargine insulin was prescribed twice daily and regular insulin by sliding scale. Although glucose control varied over the years, his renal function markedly improved and has remained stable throughout the period.

the highest risk of developing complications [16]. 2hPP glucose is the most sensitive and highly predictable glycemic parameter for the diagnosis of diabetes as reported by several authors [16, 17, 18]. Further, it has been reported that correction of postprandial hyperglycemia is likely to provide very significant benefits in reducing chronic complication of diabetes [17].

There is a robust association between 2hPP hyperglycemia and cardiovascular disorders [19]. However, information of 2hPP hyperglycemia with regard to renal function changes is scarce [20, 21]. Therefore the objective of the current study is to fill that gap. Thus, our study is fundamentally different from other studies in two ways: 1) a new paradigm of therapy 2) exclusion of the use of ACEI/ARB drugs. There are no systematic studies on paradigm of therapy like ours in treating diabetes available in the literature. An occasional report states that detemir can be used twice daily if needed [22]. It is evident that the authors' patients do and feel well, hence they are compliant in going to the laboratory twice on the same day for the prescribed tests and return to the office as scheduled. It is reported that most patients feel better when their glucose levels are under good control, which is a major driving force for the patients to accept and adhere to insulin injections. The anticipated reduction of diabetic complications further enhances their compliance [22].

Authors experience that anticipation of going into dialysis is the worst fear among the patients with diabetes. Thus, authors are convinced from this study and the previous study [11] that diabetes patients have no reason to fear dialysis if they are treated as elaborated in this study. An important question is why are so many patients entering into dialysis clinics? A chief reason for ESRD and dialysis in diabetes is excessive controversy in defining and treating diabetes. Although emphasis was given repeatedly on the benefits of adequate glucose control, and blood pressure and lipid controls in the prevention of microvascular and macrovascular complications by numerous authors [7-10, 20-23], the pendulum has swung to aggressive treatment of microalbuminuria with ACEI/ARB drugs. These drugs were put on the top as renoprotective therapy in diabetes [24-25]. Thus glycemic control had been pushed to the back seat. Use of ACEI/ARB drugs is associated with recurrent attacks of acute renal failure and eventual progression to ESRD, as reported by these and other authors [5-6, 13, 26]. In addition, as stated earlier, patients were referred for diabetes, hypertension and renal insufficiency. At the time of referral, they commonly had CKD stages 1-3 but after discontinuation of ACEI/ARB drugs renal function improved over time. Thus a big difference exists between our study where glycemic control is emphasized for renal protection compared to other studies where no attention was paid to glycemic control but ACEI/ARB drugs were excessively used to afford renal protection in diabetes. Therefore, it is prudent to state that ACEI/ARB drugs have contributed to the progression of CKD into ESRD.

Although our focus was to keep 2hPP glucose less than 11.1 mmol/L, goal was not achieved in this study. Notwithstanding elevation of 2hPP glucose above 11.1 mmol/L, in most patients, it is evident that intensive insulin therapy affords renal protection. Hence, renal function remains unchanged or improved in all patients. In this context, it is noteworthy from our cell culture studies that glucose in the culture media may not change by the addition of insulin, but endothelial cell damage is mitigated in the presence of insulin. Thus a plausible explanation is that insulin has a protective effect on organ function which may not be entirely dependent on glucose lowering effect [27].

4. CONCLUSION

This study describes diabetes patients treated with intensive insulin therapy for glycemic control and blood pressure control with antihypertensive drug therapy which excludes ACEI/ARB drugs. Glycemic control is not perfect but blood pressure control is achieved at expected level. Although this study comprises of a small number of patients and has a limited duration of follow-up, nevertheless, the paradigm of therapies used are provocative of renal protection in diabetes. Therefore, this study has permitted the authors to validate that ACEI/ARB drug therapy results in high incidence of ESRD and dialysis in a clandestine fashion.

ACKNOWLEDGEMENTS

Abstract: Linda Hiebert and Anil Mandal
Discussion: Anil Mandal
Statistical Analysis: Harry Khamis

The authors are very grateful to staff of the clinical laboratory of Putnam Community Medical Center, Palatka, Florida, USA for outstanding laboratory support for the diabetes study. Authors are fortunate to have the cooperation of all patients in undertaking repetitive laboratory studies and office visits to help them live a healthy life and not worry about dialysis.

CONFLICT OF INTEREST STATEMENT

None.

REFERENCES

1. Zimmet, P., Alberti, K. G. and Shaw, J. 2001, Nature, 414, 782.
2. Atkins, R. C. and Zimmet, P. 2010, Am. J. Kidney Dis., 55, 205.
3. Couser, W. G., Remuzzi, G., Mendis, S. and Tonelli, M. 2011, Kidney Int., 80, 1258.
4. Johansen, K. L. 2011, Arch. Intern. Med., 171, 107.
5. Mandal, A. K., Markert, R. J., Saklayen, M. G., Mankus, R. A. and Yokokawa, K. 1994, Clin. Nephrol., 42, 170.
6. Mandal, A. K. and Hiebert, L. M. 2008, Clin. Nephrol., 69, 169.
7. Ohkubo, Y., Kishawa, H., Araki, E., Miyata, T., Isami, S., Motoyoshi, S., Kojima, Y., Furuyoshi, N. and Shichiri, M. 1995, Diabetes Res. Clin. Pract., 28, 103.
8. Reichard, P., Nilsson, B. Y. and Rosenqvist, U. 1993, N. Engl. J. Med., 329, 304.
9. The Diabetes Control and Complications Trial Research Group. 1993, N. Engl. J. Med., 329, 977.
10. Fabre, J., Balant, L. P., Dayer, P. G., Foz, H. M. and Vernet, A. T. 1982, Kidney Int., 21, 730.
11. Mandal, A. K., Hiebert, L. M. and Khamis, H. 2011, Diab. Res. Clin. Pract., 91, 190.
12. National Diabetes Data Group. 1979, Diabetes, 28, 1039.
13. Mandal, A. K. 2010, Int. J. Urol. Nephrol., 2, 567.
14. Woodhouse, S., Batten, W., Hendrick, H. and Malek, P. A. 2006, Lab. Med., 37, 244.
15. Mandal, A. K. and Neki, N. S. 2011, OJIM, 1, 93.
16. Harris, M. I. 1993, Diabetes Care, 16, 642.
17. Levovitz, H. E. 1998, Diab. Res. Clin. Pract., 40(Suppl.), S27.
18. McCance, D. R., Hanson, R. L., Charles, M. A., Jacobsson, L. T. H., Pettit, D. J., Bennett, P. H. and Knowler, W. C. 1994, BMJ, 308, 1323.
19. Qiao, Q., Pyorala, K., Pyorala, M., Nissinen, A., Lindstrom, J., Tilvis, R. and Tuomileh, J. 2002, Eur. Heart J., 23, 1267.
20. Nosadini, R. and Tonolo, G. 2004, J. Am. Soc. Nephrol., 15(Suppl.), S1.
21. Rasmussen, B. F. 2000, Diab. Obesity Met., 2(Suppl.), S13.
22. Hamaty, M. 2011, Clev. Clin. J. Med., 78, 332.
23. Holman, R. R., Paul, S. K., Bethel, M. A., Mathews, D. R. and Neil, H. A. 2008, N. Engl. J. Med., 359, 1577.
24. Lewis, E. J., Hunsicker, L. G., Baiu, R. P. and Rohde, R. D. 1993, N. Engl. J. Med., 329, 1456.
25. Brenner, B. M., Cooper, M. E., deZee, U. W. D., Keane, W. F., Mitch, W. E., Parving, H. H., Remuzzi, G., Snapinn, S. M., Zhang, Z. and Shahinpar, S. 2001, N. Engl. J. Med., 354, 861.
26. Suissa, S., Hutchinson, T., Brophy, J. M. and Kezouh, A. 2006, Kidney Int., 69, 913.
27. Mandal, A. K., Ping, T., Caldwell, S. J., Bagnell, R. and Hiebert, L. M. 2006, Histol. Histopathol., 21, 941.