Original Article

Burnt-out diabetes in diabetic nephropathy patients on maintenance haemodialysis

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Abstract

Background: Diabetic nephropathy contributes to about 50% of end-stage renal disease (ESRD) worldwide. Diabetic ESRD patients experience spontaneous resolution of hyperglycaemia with normalisation of blood glucose and glycosylated haemoglobin leading to discontinuation of antidiabetic medicines, which progress to burnt-out diabetes state. The occurrence of burnt-out diabetes state needs to be identified for reducing the occurrence of hypoglycaemic episodes in diabetes patients on maintenance haemodialysis (MHD).

Methods: A cross-sectional study was conducted in ESRD patients on MHD at the dialysis unit, the Department of Nephrology at Sri Venkateswara Institute of Medical Sciences, Tirupati, during the period January–April 2016. The diabetic ESRD patients on MHD were further subgrouped as burnt-out and non-burnt-out patients.

Results: Among the patients with diabetes, burnt-out state was observed in 12 (23%) and non-burnt out were of 40 (77%) patients. The serum triglycerides, very low-density lipoprotein cholesterol, low-density lipoprotein cholesterol and parathyroid hormone levels were found to be increased, whereas body mass index, blood urea, serum high-density lipoprotein (HDL) and 25 hydroxy vitamin D (25 OHD_3) levels were found to be decreased in burnt-out diabetic patients compared with non-burnt-out diabetic patients which were not statistically significant except for urea and HDL.

Conclusion: Approximately, one-fourth of our patients were belonging to burnt-out diabetes state. If burnt-out diabetes state is recognised, unnecessary administration of insulin and other drugs which precipitate hypoglycaemia can be avoided so that the future risk of cardiovascular disease and mortality is minimised.

Keywords: Burnt-out state, end-stage renal disease, hypoglycaemia, maintenance haemodialysis

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INTRODUCTION

Diabetic nephropathy (DN) is a widely recognised common cause of the end-stage renal disease (ESRD) in patients with diabetes mellitus.[1] Patients with diabetes mellitus on maintenance haemodialysis show a dual presentation regarding the glycaemic status. Majority of them continue to manifest hyperglycaemia requiring therapies, while a minor category manifests normoglycaemia or hypoglycaemia with normalisation of glycosylated haemoglobin (HbA_{1c}) levels due to spontaneous resolution which is being known as burnt-out diabetes.[2] Burnt-out diabetes is that state in diabetic patients on maintenance dialysis who frequently experience episodes of hypoglycaemia

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which further prompt them to stop antidiabetic therapies either transiently or even permanently.[3] Hypoglycaemic interventions in this population are also complicated by the complex changes in glucose homoeostasis which are related to the decreased kidney function and dialytic therapies leading to spontaneous improvement in glucose levels and manifesting as normoglycaemia and normalisation of HbA_{1c} levels.[4] As the stages of chronic kidney disease (CKD) advance in diabetic patients, a decline in insulin requirements occurs, thus underscoring the complex nature of the uraemic dysregulation of glucose homoeostasis.[5] In patients with diabetes in addition to the direct impact of uraemia and renal insufficiency on glycaemic status, the initiation of dialysis therapy *per se* might improve insulin sensitivity and glucose tolerance.[6] Potential contributors to 'burnt-out diabetes' include decreased renal and hepatic insulin clearance, decline in renal gluconeogenesis, deficient catecholamine release, diminished food intake due to anorexia, diabetic gastroparesis, protein–energy wasting with resultant weight loss and dialysis treatment.[7] Good glycaemic control might reduce mortality in DN patients, but avoidance of hypoglycaemia is most important to prevent the high mortality rate. Hence, the present study was undertaken to assess the extent of burnt-out diabetes in diabetic ESRD patients on maintenance haemodialysis (MHD).

MATERIAL AND METHODS

This cross-sectional study was conducted at the dialysis unit, the Department of Nephrology at Sri Venkateswara Institute of Medical Sciences, Tirupati, for a duration of 4 months (January–April 2016) on ESRD patients on MHD. A total of 135 MHD patients in the time period of 4 months were identified. Among them, 52 were patients with diabetes mellitus and 83 were patients with non-diabetes. The diabetic patients on MHD were further subgrouped as burnt-out (n = 12) and non-burnt-out (n = 40) patients. Burnt-out diabetes state was described as diabetic CKD patients not requiring insulin or any other drug along with normalisation of fasting plasma glucose (FPG) <110 mg/dL, post-prandial blood sugar (PPBS) <140 mg/dL and HbA_{1c} <7%.[8] The exclusion criteria for burnt-out diabetes cases were diabetes mellitus patients on insulin or any other oral hypoglycaemic drugs, acute on CKD, history of alcohol abuse, smoking, paediatric age group (<18 years), pregnant women, vasculitis, liver disease, malignancy and unwilling patients.

Laboratory analysis

Data were recorded for various clinical, biochemical indices and treatment modalities from ESRD patients on MHD. Data were collected and recorded for age, gender, height, weight and body mass index (BMI) in these patients.

Data for the following relevant biochemical parameters were also recorded. FPG and PPBS were estimated by the glucose oxidase-peroxidase method. Serum urea and creatinine were estimated by timed fixed endpoint method and Modified Jaffe's rate kinetic method, respectively, using Beckman system pack. Serum total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and albumin were estimated using commercial kits. Low-density lipoprotein cholesterol (LDL-C) and very LDL-C were calculated by Friedewald's equation. All the above parameters were analysed on the Beckman Coulter UniCel DxC 600 clinical chemistry autoanalyser, USA. HbA_{1c} was estimated using ion-exchange high-performance liquid chromatography method. Parathyroid hormone was estimated by chemiluminscence assay and Vitamin D was estimated by immunoradiometric assay on the Beckman analyser.

Statistical analysis

All continuous variables were tested for normal distribution with the Kolmogorov–Smirnov test. Normally distributed data were presented as the mean ± standard deviation. Categorical data were presented as numbers and per cent. Comparisons between the groups were analysed using independent Student's t-test. All statistical analyses were performed with SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

In the present study, among 135 MHD patients, 52 (38%) of them were diabetic and 83 (62%) were non-diabetic. Among 52 diabetic patients on MHD, 12 (23%) of them belong to burnt-out diabetes group and 40 (77%) of them belong to non-burnt-out diabetes group. The general demographic and clinical characteristics of burnt-out and non-burnt-out diabetic ESRD patients on haemodialysis were shown in Table 1. The demographic and clinical characteristics of burnt-out and non-burnt-out diabetic ESRD patients on MHB were similar (P = NS). The average duration to withdraw insulin treatment in burnt-out diabetic ESRD patients on dialysis was found to be approximately 2–3 years. Presence of co-morbid conditions in both the groups was shown in Table 2. Co-morbid conditions in both the groups were found to be non-significant ($P > 0.05$). The comparison of means in between the two groups using independent Student's t-test was shown in Table 3.

Table 1: Clinical characteristics of the patients

Variables	Burnt-out diabetic group (*n*=12)	Non-burnt-out diabetic group (*n*=40)	*P*
Age (years)	61.5±7.4	62.6±6.76	0.62
Male:female	11:1	23:7	0.30
BMI (kg/m^2)	21.8±1.7	23.7±4.4	0.03
Duration of DM (years)	18.8±7.6	16.6±8.6	0.41
Duration of HTN (years)	8.9±5.4	9.5±6.9	0.75
Duration of OHA therapy (years)	11.2±7.0	9.8±8.1	0.56
Duration of insulin therapy (years)	6.4±4.1	6.7±4.2	0.82
MHD vintage (years)	3.9±2.30	3.0±1.8	0.26

BMI=Body mass index; DM=Diabetes mellitus; HTN=Hypertension; OHA=Oral hypoglycaemic agents; MHD=Maintenance haemodialysis

Table 2: Co-morbid conditions

Variables	Burnt-out diabetic group (*n*=12), *n* (%)	Non-burnt diabetic group (*n*=40), *n* (%)	*P*
DR	75	87.5	0.33
DSPN	33.3	62.5	0.53
CVA	16.7	20	0.95
CAD	33.3	30	0.95

DR=Diabetic retinopathy; DSPN=Distal sensory polyneuropathy; CVA=Cerebrovascular accident; CAD=Coronary artery disease

Table 3: Comparison of mean±standard deviation of the biochemical parameters in both the groups using unpaired *t*-test

Parameter	Burnt-out diabetic group (*n*=12)	Non-burnt diabetic group (*n*=40)	*P*
FPG (mg/dL)	106.8±15.7	138.7±45.3	0.02
PPBS (mg/dL)	151.9±19.9	187.8±60.5	0.03
Serum urea (mg/dL)	108.2±50.7	149.9±6.3	0.04
Serum creatinine (mg/dL)	8.9±1.5	11.2±5.5	0.35
Serum albumin (g/dL)	3.9±0.5	3.9±0.6	0.85
Serum 25 OH D3 (ng/mL)	22.3±11.2	25.4±19.3	0.48
Serum PTH (pg/mL)	192.8±93.1	153.5±19.3	0.29
Serum CHOL (mg/dL)	143.3±17.9	153.5±61.8	0.15
Serum TGL (mg/dL)	154.7±46.4	137.8±51.6	0.29
Serum HDL-C (mg/dL)	30.7±10.5	47.7±37.6	0.01
Serum VLDL-C (mg/dL)	30.9±9.3	27.6±10.3	0.32
Serum LDL-C (mg/dL)	81.2±16.7	78.2±32.7	0.76
HbA_{1c} (%)	6.1±1.5	7.7±0.8	0.001

FPG=Fasting plasma glucose; PPBS=Post-prandial blood sugar; CHOL=Cholesterol; TGL=Triglycerides; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; VLDL=Very low-density lipoprotein; HbA_{1c}=Glycosylated haemoglobin; PTH=Parathyroid hormone

The mean FPG was 106.8 ± 15.7 mg/dL and the mean post-prandial sugar was 151.9 ± 19.9 mg/dL with a mean HbA_{1c} was 6.1% in burnt-out diabetic group compared with non-burnt-out diabetic group which was found to be statistically significant ($P < 0.001$). Burnt-out patients had lower BMI, urea and HDL compared to non-burnt group. The remaining biochemical parameters were found to be non-significant (P = NS) except for blood urea and HDL-C which were found to be statistically significant ($P = 0.04$ and $P = 0.01$ respectively).

DISCUSSION

'Burnt-out diabetes' is a biologic entity in ESRD diabetic patients on MHD. In the present study, the following observations as BMI, HbA_{1c}, serum albumin, total cholesterol, LDL-C and triglyceride levels were found to be normal or near normalcy range in burnt-out patients. As evidenced by the above findings in the present study, there was no evidence to suggest malnutrition in burnt-out group. However, burnt-out group had low HDL. Diabetes is one of the most important causes of CKD. Gradual decline in kidney function itself causes significant changes that alter glucose homoeostasis in patients with kidney disease.[9] A study[10] reported that the reason for the abnormal glucose homoeostasis in patients with CKD was multifactorial and involves various mechanisms related to both decreased kidney function and dialytic therapies. Renal clearance of insulin is diminished as the glomerular filtration rate declines. Hepatic clearance of insulin also tends to decline in uraemia, although it may improve after the initiation of dialysis.[11] Nevertheless, an increase in insulin resistance and decrease in insulin secretion may happen in more advanced CKD stages, which are related to secondary hyperparathyroidism and vitamin D deficiency. However, in the present study, no significant difference in the concentrations of parathyroid hormone and vitamin D levels between both the groups was observed which could not explain the cause for decreased renal clearance.

Another study,[12] on 23,618 diabetic patients on MHD, reported that dialysis patients with low HbA_{1c} levels suffer significantly higher mortality rates, thus emphasising the need to relate burnt-out diabetes as a complication of a disease (ESRD) rather than as a benefit of it.[12] By reviewing the literature, monitoring of HbA_{1c} levels for management of diabetic patients on dialysis should be encouraged and appropriate target ranges specific for these patients should be specified. The current recommended HbA_{1c} target for glycaemic control in diabetic patients that is, HbA_{1c} below 6.5% or 7%, was derived from the studies in diabetic population without renal insufficiency.[13] The HbA_{1c} measurement can be confounded in the uraemic *milieu* and henceforth the characterisations of the pathophysiology and the clinical impact of burnt-out diabetes represent a

major challenge for future clinical research. All the above findings suggest that overcorrection of hyperglycaemia can induce hypoglycaemia and significantly worsen the outcomes. Hence, it is essential to determine the clinical impact of burnt-out diabetes state on spontaneous improvement in blood glucose levels.

Any efforts to treat hyperglycaemia in diabetic ESRD patients on MHD must take into account the complex changes in glucose and insulin metabolism, effect of decreased renal function on the pharmacokinetics of medications and type of renal replacement therapy. The state of burnt-out diabetes should be recognised to avoid unnecessary administration of insulin and other drugs which further minimise the occurrence of hypoglycaemic episodes. Careful monitoring and individualised therapy are recommended to achieve good glycaemic control in burnt-out diabetes patients on MHD.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lim AK. Diabetic nephropathy – Complications and treatment. Int J Nephrol Renovasc Dis 2014;7:361-81.
2. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N, Wu DY. Reverse epidemiology: A spurious hypothesis or a hardcore reality? Blood Purif 2005;23:57-63.
3. Kovesdy CP, Sharma K, Kalantar-Zadeh K. Glycemic control in diabetic CKD patients: Where do we stand? Am J Kidney Dis 2008;52:766-77.
4. Kalantar-Zadeh K, Derose SF, Nicholas S, Benner D, Sharma K, Kovesdy CP. Burnt-out diabetes: Impact of chronic kidney disease progression on the natural course of diabetes mellitus. J Ren Nutr 2009;19:33-7.
5. Mak RH. Impact of end-stage renal disease and dialysis on glycemic control. Semin Dial 2000;13:4-8.
6. Schmitz O. Insulin-mediated glucose uptake in nondialyzed and dialyzed uremic insulin-dependent diabetic subjects. Diabetes 1985;34:1152-9.
7. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, *et al*. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int 2006;70:771-80.
8. Park J, Lertdumrongluk P, Molnar MZ, Kovesdy CP, Kalantar-Zadeh K. Glycemic control in diabetic dialysis patients and the burnt-out diabetes phenomenon. Curr Diab Rep 2012;12:432-9.
9. Morioka T, Emoto M, Tabata T, Shoji T, Tahara H, Kishimoto H, *et al*. Glycemic control is a predictor of survival for diabetic patients on hemodialysis. Diabetes Care 2001;24:909-13.
10. Kovesdy CP, Park JC, Kalantar-Zadeh K. Glycemic control and burnt-out diabetes in ESRD. Semin Dial 2010;23:148-56.
11. Oomichi T, Emoto M, Tabata T, Morioka T, Tsujimoto Y, Tahara H, *et al*. Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: A 7-year observational study. Diabetes Care 2006;29:1496-500.
12. Kalantar-Zadeh K, Kopple JD, Regidor DL, Jing J, Shinaberger CS, Aronovitz J, *et al*. A1C and survival in maintenance hemodialysis patients. Diabetes Care 2007;30:1049-55.
13. Nathan DM, Bayless M, Cleary P, Genuth S, Gubitosi-Klug R, Lachin JM, *et al*. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: Advances and contributions. Diabetes 2013;62:3976-86.