

## ORIGINAL ARTICLE



# Glycemic Patterns and Factors Associated with Post-Hemodialysis Hyperglycemia among End-Stage-Renal Disease Patients undergoing Maintenance Hemodialysis\*

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## Abstract

**Introduction.** Chronic and post-prandial hyperglycemia are independent risk factors for diabetic complications. Glycemic patterns among hemodialysis end-stage-renal-disease (ESRD) differ as glucose metabolism changes with declining kidney function with more pronounced glycemic fluctuations. The objectives of this study are to determine glycemic patterns on hemodialysis days, the magnitude of post-hemodialysis rebound hyperglycemia (PHH) and their associated factors.

**Methodology.** 148 patients on hemodialysis were analysed, 91 patients had end-stage-diabetic-renal disease (DM-ESRD), and 57 patients had end-stage-non-diabetic renal disease (NDM-ESRD). Glycemic patterns and PHH data were obtained from 11-point and 7-point self-monitoring blood glucose (SMBG) profiles on hemodialysis and non-hemodialysis days. PHH and its associated factors were analysed with logistic regression.

**Results.** Mean blood glucose on hemodialysis days was 9.33 [SD 2.7] mmol/L in DM-ESRD patients compared to 6.07 [SD 0.85] mmol/L in those with NDM-ESRD ( $p < 0.001$ ). PHH occurred in 70% of patients and was more pronounced in DM-ESRD compared to NDM-ESRD patients (72.5% vs 27.5%; OR 4.5). Asymptomatic hypoglycemia was observed in 18% of patients. DM-ESRD, older age, previous IHD, obesity, high HbA1c, elevated highly-sensitive CRP and low albumin were associated with PHH.

**Conclusion.** DM-ESRD patients experienced significant PHH in our cohort. Other associated factors include older age, previous IHD, obesity, high HbA1c, elevated hs-CRP and low albumin.

**Key words:** renal dialysis, glycemic variability, diabetes complications, hyperglycemia, risk factors

## INTRODUCTION

Over two million people worldwide currently on renal replacement therapy have Type 2 Diabetes Mellitus (T2DM), the leading cause of end-stage-renal-disease (ESRD).<sup>1,2</sup> In Malaysia T2DM accounted for 61% of new dialysis patients.<sup>3</sup>

Glycemic patterns among diabetic patients with ESRD (DM-ESRD) whether or not on hemodialysis differ from those of diabetic patients without ESRD as glucose metabolism changes with decline in kidney function. Glycemic fluctuations are more pronounced among DM-ESRD as they may experience hemodialysis induced hypoglycemia and hyperglycemia.<sup>4,5</sup> Furthermore, hemodialysis per se is an independent risk factor for glycemic fluctuations as glucose is freely filtered and insulin is absorbed during hemodialysis.<sup>6</sup>

Fluctuations in glucose metabolism have proven to be detrimental in DM-ESRD as they leads to poor survival mainly owing to cardiovascular complications.<sup>7</sup> This was demonstrated by a six-year cohort study among DM-ESRD patients that showed a U-shape association between glycemic control (HbA1c  $< 6\%$  and  $> 8\%$ ) and a decrease in overall survival.<sup>8</sup> This U-shape association might indicate that chronic hyperglycemia is not the only indicator for morbidity and mortality, but also hypoglycemia and glucose fluctuations.<sup>7,8</sup> Furthermore, many studies have shown glycemic variability (GV) as an independent risk factor for both morbidity and mortality among diabetic populations.<sup>9</sup>

Therefore, this study focused on glycemic patterns on hemodialysis days and non-hemodialysis days among ESRD patients. We also looked at post-hemodialysis rebound hyperglycemia (PHH), and its associated factors, as identifying these factors is hoped to optimize the management of this high-risk group.

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## METHODOLOGY

### Study design and sample population

One hundred and fifty ESRD patients on maintenance hemodialysis (93 DM-ESRD patients and 57 NDM-ESRD patients), were recruited in this cross-sectional study. Sample size was calculated by multiple logistic regression using G Power software.<sup>10</sup> Based on a study by Jin Y.P, 2015 we estimate the occurrence of post haemodialysis hyperglycemia among the DM-ESRD patients to be threefold that of NDM-ESRD patients.<sup>11</sup> We considered a model with one binary covariate  $X$  with event rate under  $H_0$ ,  $p_1 = 0.13$  and the event rate under  $X = 1$ ,  $p_2 = 0.40$ , giving the odds ratio of  $\sim 4.5$ . We further assumed  $R^2 = 0.1$ , and an imbalanced design ratio of 2:1 between the 2 groups. The estimating sample size necessary to achieve a two-sided test with alpha of 0.05 and power of at least 80% was 102. Considering a 30% non-response rate, the final sample size was 146 rounded to 150.

Inclusion criteria were: adults age more than 18 with or without diabetes, patients on maintenance hemodialysis for at least three months. NDM-ESRD patients were included to observe the effect of hemodialysis on non-diabetic patients. Exclusion criteria were: Type 1 diabetes mellitus patients, presence of acute inflammatory state, hemoglobinopathy, history of blood transfusion or hospitalization for the last three months, and diagnosis of malignancy.

### Socio-demographics, co-morbidities and laboratory data

Socio-demographic characteristics, clinical data, co-morbidities and medication lists were obtained using a standardized questionnaire. At recruitment, baseline blood investigations were taken: glycated hemoglobin –A1c (HbA1c), lipid profile, renal profile, albumin, hemoglobin, inflammatory markers, iron studies and bone parameters.

### Glucose monitoring on hemodialysis and non-hemodialysis days

Glucose values in our study were obtained from capillary glucose measurements using capillary glucometers (Bayer contour plus®). Patients were taught to self-measure the capillary glucose and were assisted during the hemodialysis sessions. Patients were advised to record the glucose values and medications taken and were also educated to recognize hypoglycemic signs and symptoms. On hemodialysis days, a 11-point capillary self-monitoring glucose (SMBG) profile was obtained with hourly capillary glucose taken during the hemodialysis sessions. On non-hemodialysis days, 7 points SMBG were taken by the patients. Patients were not required to fast during hemodialysis but were asked to report and food consumed that was out of their ordinary diet.

### Statistical analysis

Analyses were performed using R studio version 1.0.153 using the STATS package for statistical analysis. In descriptive statistics, categorical data results were described as count and percentage while continuous data in mean and standard deviation (SD). Overall glycemic profile, specifically looking, as post hemodialysis glucose value was measured in terms of means glucose  $\pm$  SD. The data was checked for normality visually by histogram

and statistically using the Shapiro Wilk test. For bivariate analysis, a chi squared test was used for comparing categorical data. An independent t-test was used to compare means between the groups as the data was normally distributed. The assumption of equal variance was met using Levene's test. The level of significance was set at 0.05. In order to determine the association between PHH with clinical and laboratory variables, simple logistic regression was done to derive the crude odd ratio. Subsequently, the variables which were significant at  $p < 0.15$  were included in the final multivariate logistic regression analysis. All the crude and adjusted odds ratios were presented with 95% confidence intervals. For missing data, the Listwise deletion method was used.

## RESULTS

### Socio-demographics, co-morbidities and laboratory data analysis

From the total of 150 patients recruited, 148 patients data were included in the final analysis due to missing data from two patients. Table 1 demonstrates the baseline sociodemographics and co-morbidities of our cohort. Ninety-one (61.5%) patients had diabetes with a mean age of 57.6 years and mean duration of diabetes of 16.4 years. Mean duration of hemodialysis in DM-ESRD and NDM-ESRD patients were 3.8 and 4.5 years, respectively. Body mass index (BMI) in the majority of patients was Obese Class 1. The difference in socio-demographics and co-morbidities among both groups were not statistically significant apart from DM-ESRD patients having higher BMI and higher prevalence of smoking among NDM-ESRD patients. Ischemic heart disease (IHD) was present in one-fourth of the patients. Blood pressure control was poor with only 16 (10.7%) of DM-ESRD and 47 (31.3%) of NDM-ESRD patients achieving pre and post hemodialysis target blood pressure of less or equal to 130/80 mmHg.

In terms of medications, 50 (54.9%) of diabetic patients were on insulin therapy, 18 (19.7%) on oral hypoglycemic agents (OHA), and 23 (25.2%) were not on regular medications. The majority of patients, i.e., 56 (82.3%) patients, would not take their medications on hemodialysis days. Patients on OHA alone would not take their OHA on hemodialysis days, while patient on basal-bolus insulin, would omit the insulin dose before their hemodialysis session.

Table 2 compares the baseline blood parameters between DM-ESRD and NDM-ESRD patients. Both groups had a non-significant difference in terms of blood parameters apart from HbA1c, phosphate and albumin. Mean HbA1c among DM-ESRD patients was 7.4% with 37% having HbA1c less than 6.5% and 30% falling between 6.5% to 8%. Analysing the highly sensitive C-reactive protein (hs-CRP) as a surrogate marker for cardiac disease showed both groups having high hs-CRP levels with means of 8.91mg/L and 7.03 mg/L among DM-ESRD and NDM-ESRD patients respectively. Albumin levels were significantly lower among DM-ESRD patients, while phosphate levels were higher among NDM-ESRD patients.

In our DM-ESRD cohort, 13 (14.3%) took their OHA/insulin on hemodialysis days with 3 (3.3%) of patients reporting hypoglycemic symptoms during hemodialysis sessions. Almost all (94.7%) patients ate during hemodialysis.

**Table 1.** Baseline socio-demographic and clinical characteristics of patients

Characteristics	DM-ESRD n (%)	NDM-ESRD n (%)	Test statistic*	p value
<b>Sex</b>			0.165	0.685
Male	51 (56.0)	30 (52.6)		
Female	40 (44.0)	27 (47.4)		
<b>Race</b>			1.078	0.583
Malay	79 (86.8)	52 (91.2)		
Chinese	1 (1.1)	1 (1.8)		
Indian	11 (12.8)	4 (7.0)		
<b>BMI</b>			10.729	<b>0.030***</b>
Underweight (<18.5)	1 (1.1)	4 (7.0)		
Normal (18.5 – 22.9)	11 (12.8)	15 (26.3)		
Overweight (23.0 – 24.9)	15 (16.5)	7 (12.3)		
Obese Class 1 (25.0 – 29.9)	41 (45.1)	16 (28.1)		
Obese Class 2 (>30.0)	23 (25.3)	15 (26.3)		
<b>BP Target Pre HD</b>			1.383	0.240
Pre-HD BP (≤130/80)	12 (13.2)	4 (7.0)		
Pre-HD BP (>130/80)	79 (86.8)	53 (93.0)		
<b>BP Target Post HD</b>			3.426	0.064
Post HD BP (≤130/80)	34 (37.4)	13 (22.8)		
Post HD BP (>130/80)	57 (62.6)	44 (77.2)		
<b>Smoking</b>			7.074	<b>0.008***</b>
Yes	4 (4.4)	10 (17.5)		
No	87 (95.6)	47 (82.5)		
<b>Hypertension</b>			2.311	0.128
Yes	90 (98.9)	54 (94.7)		
No	1 (1.1)	3 (5.3)		
<b>IHD</b>			1.038	0.308
Yes	26 (28.6)	12 (21.1)		
No	65 (71.4)	45 (78.9)		
<b>Gout</b>			1.415	0.234
Yes	6 (6.6)	7 (12.3)		
No	85 (93.4)	50 (87.7)		
<b>Stroke</b>			0.307	0.580
Yes	5 (5.5)	2 (3.5)		
No	86 (94.5)	55 (96.5)		
<b>Hyperlipidaemia</b>			2.857	0.091
Yes	56 (61.5)	27 (47.4)		
No	35 (38.5)	30 (52.6)		
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Test statistic**</b>	<b>P value</b>
Age (years)	57.6 (11.1)	49.0 (11.2)	-4.590	<b>&lt;0.001***</b>
Duration of HD (years)	3.8 (3.1)	4.5 (3.3)	1.310	0.198
BMI (kg/m <sup>2</sup> )	27.1 (4.4)	26.2 (6.6)	-0.862	0.391

Table 1 shows the baseline sociodemographic and clinical characteristics of patients (n=148), values expressed as mean ± standard deviation. DM-ESRD, diabetic-end stage renal disease; NDM-ESRD, non diabetic end-stage-renal-disease; HD, hemodialysis; BP, blood pressure; BMI, body mass index. \*Chi square test \*\*Independent t-test \*\*\*P value<0.05

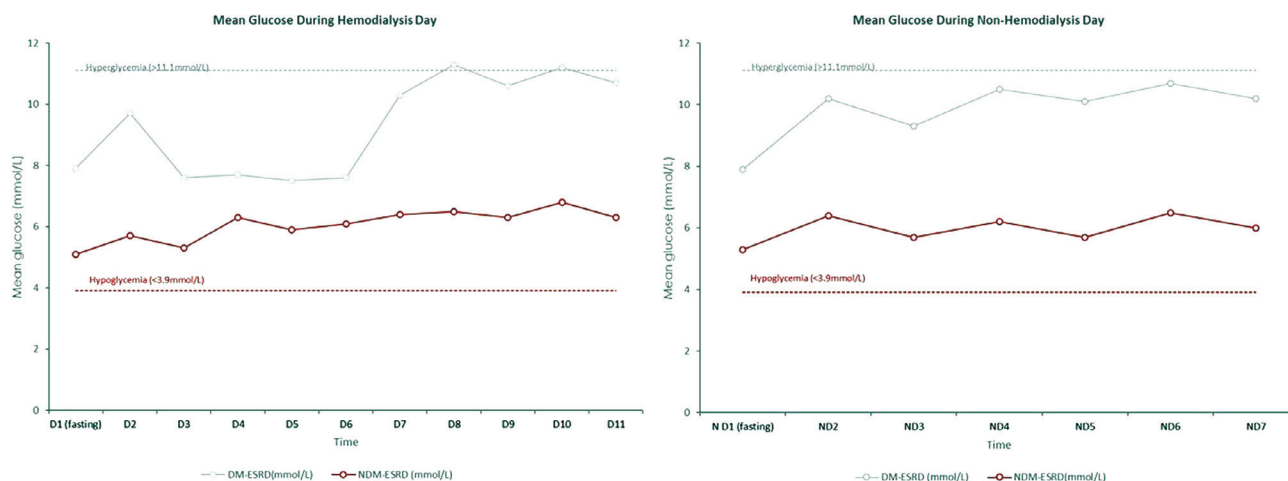
**Table 2.** Mean (SD) blood parameters comparing DM-ESRD and NDM-ESRD

Characteristics	DM-ESRD Mean (SD)	NDM-ESRD Mean (SD)	T statistic	P value
Hemoglobin (g/dL)	10.47 (1.7)	10.38 (1.7)	-0.339	0.735
HbA1c (%)	<b>7.40 (1.6)</b>	5.41 (0.5)	-10.845	<b>&lt;0.001*</b>
Total cholesterol (mmol/L)	4.8 (1.3)	5.0 (1.2)	1.003	0.318
LDL (mmol/L)	2.97 (1.16)	3.10 (1.18)	0.664	0.508
TG (mmol/L)	2.30 (1.7)	2.04 (1.4)	-1.030	0.304
HDL (mmol/L)	0.97 (0.22)	1.08 (0.29)	2.560	0.012
HSCRP (mg/L)	8.91 (10.2)	7.03 (7.1)	-1.310	0.192
Ferritin (ug/L)	554.1 (402)	665.2 (435)	1.497	0.137
Transferrin saturation (%)	23.96 (11.2)	24.82 (8.8)	0.526	0.600
Calcium (mmol/L)	2.16 (0.22)	2.19 (0.24)	0.883	0.379
Phosphate (mmol/L)	1.85 (0.54)	2.18 (0.73)	<b>2.893</b>	<b>0.005*</b>
iPTH (pmol/L)	73.6 (58.3)	103.7 (105.1)	1.889	0.063
ALP (U/L)	176.32 (173.3)	143.37 (112.2)	-1.413	0.159
Albumin (mmol/L)	<b>38.3 (4.2)</b>	40.1 (2.7)	3.190	<b>0.002*</b>

Table 2 shows the baseline blood parameters of patients (n=148), values expressed as mean ± standard deviation. HbA1c, glycolated hemoglobin A1c; LDL, low density lipoprotein; TG, triglycerides; HDL, high density lipoprotein; HSCRP, highly sensitive C-reactive protein; iPTH, intact parathyroid hormone; ALP, alkaline phosphatase. \* p < 0.05.

Figure 1 illustrates mean blood glucose on hemodialysis days, which were significantly different ( $p<0.01$ ) between DM-ESRD and NDM-ESRD patients. The mean ( $\pm$ SD) blood glucose was  $9.33\pm 2.7$  mmol/L in DM-ESRD and  $6.07\pm 0.85$  mmol/L in NDM-ESRD. The mean fasting blood glucose was 7.9 mmol/L and 5.1 mmol/L in DM-ESRD and NDM-ESRD patients, respectively.

During the intra-dialytic period, the mean blood glucose was 8.1 mmol/L and 5.9 mmol/L in DM-ESRD and NDM-ESRD groups, respectively. Among DM-ESRD, 61 (67.0%) of patients had readings within the suggested limits (4.4–8.5 mmol/L). Thirty (32.9%) patients recorded blood glucose more than 8.5 mmol/L. Among NDM-ESRD patients, the majority recorded values within the suggested



**Figure 1.** Glycemic patterns among DM-ESRD vs. NDM-ESRD during hemodialysis days and non-hemodialysis days.

Legend: DM-ESRD shows more marked glucose fluctuations during hemodialysis days with prominent post-hemodialysis hyperglycemia coupled with persistent hyperglycemia until the end of the day. Glycemic fluctuations were not prominent during non-hemodialysis days in both DM-ESRD and NDM-ESRD. Timing hemodialysis day: D1 = Fasting, D2 = Prior hemodialysis, D3 = 1<sup>st</sup> hour hemodialysis, D4 = 2<sup>nd</sup> hour hemodialysis, D5 = 3<sup>rd</sup> hour hemodialysis, D6 = 4<sup>th</sup> hour hemodialysis, D7 = 2 hours post hemodialysis, before meal, D8 = 2hrs post meal, D9 = before dinner, D10 = 2 hours post dinner, D11= before sleep. Timing non-hemodialysis: ND1 = Fasting – before breakfast, ND2 = 2 hours post breakfast, ND3 = before lunch, ND4 = 2 hours post lunch, ND5 = before dinner, ND6 = 2 hours post dinner, ND7 = before sleep.

intradialytic glucose limits. Eighteen (12%) patients i.e. 7 (7.6%) with DM-ESRD and 11 (19.3%) with NDM-ESRD, experienced intradialytic asymptomatic hypoglycemia. This phenomenon which was seen predominantly among NDM-ESRD patients occurred mainly during the first hour of hemodialysis with mean pre-hemodialysis blood glucose of 4.3 mmol/L among NDM-ESRD patients.

Post-hemodialysis trends showed a mean pre-prandial reading among DM-ESRD patients of 10.4 mmol/L and a mean post-prandial reading of 11.1 mmol/L. Among DM-ESRD patients, 70 (77%) had blood glucose of more and equal to 7.0 mmol pre-prandially, while 65 (72%) had blood glucose more than 8.0 mmol/L post-prandially. Figure 1 shows that the DM-ESRD group had persistently high glucose level post-hemodialysis until the end of the day, which was not seen in the NDM-ESRD group.

**Post-hemodialysis hyperglycemia (PHH)**

PHH (defined as blood glucose  $\geq 11.1$  mmol/L 2-hours after first meal) post hemodialysis was prominent among DM-ESRD patients, as almost 75 (82.4%) of them experienced more than 80% increase of blood sugar, compared to NDM-ESRD patients during the end of hemodialysis, odds ratio 4.5 (CI: 2.2 – 9.6) (Figure 2). However, among NDM-ESRD patients, almost half of the patients, i.e. 25 (43.8%) experienced a reduction in blood sugar post hemodialysis as compared to only 14 (15.4%) of DM-ESRD patients.

**Glycemic pattern on non-hemodialysis days**

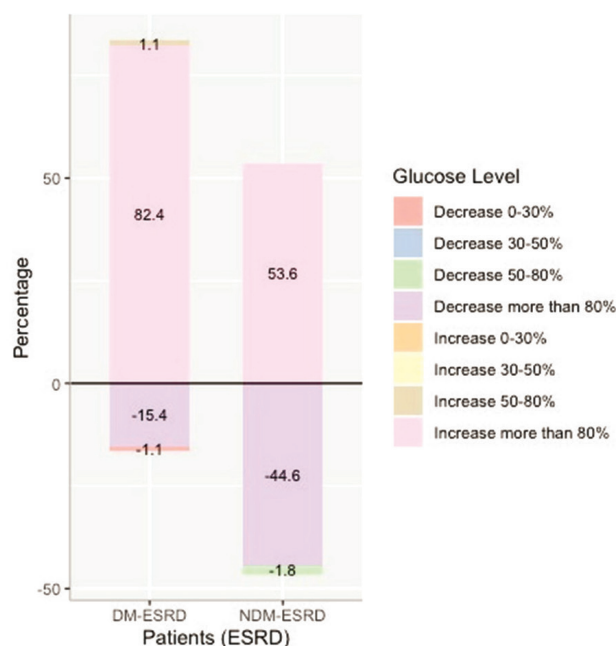
On non-hemodialysis days (Figure 1), there were significant differences between blood sugar profiles among DM-ESRD and NDM-ESRD patients, where the mean (SD) blood glucose was  $9.85 \pm 3.1$  mmol/L and  $6.0 \pm 0.88$  mmol/L, respectively. In DM-ESRD patients, post-prandial hyperglycemia more or equal to 8.5 mmol/L were observed in 61 (67.0%) patients with 28 (30.8%) experiencing blood sugar more or equal to 11.1 mmol/L (mean preprandial  $9.1 \pm 3.1$  mmol/L and post-prandial  $10.4 \pm 3.3$  mmol/L).

**Correlation between mean blood glucose and HbA1c**

In our population, there was a strong correlation between mean blood glucose and HbA1c among all patients with  $R^2 = 0.73$ . However, among DM-ESRD patients, the correlation was moderate with  $R^2 = 0.59$ .

**Factors associated with PHH**

Table 3 demonstrates a simple logistic regression analysis of clinical characteristics and blood parameters associated with PHH. In this study, DM-ESRD, obesity, previous IHD, older age, high HbA1c, elevated hs-CRP and low



**Figure 2.** Capillary glucose changes post hemodialysis sessions

Legend: Figure 2 showing the capillary glucose changes occurs post hemodialysis session between DM-ESRD and NDM-ESRD. In DM-ESRD, 75 (82.4%) experienced more than 80% increased of blood sugar value, compared to NDM-ESRD during the end of hemodialysis with odds ratio of 4.5 (CI: 2.2 – 9.6).



**Table 3.** Factors associated with post haemodialysis hyperglycaemia (PHH) using simple logistic regression

	PHH		Test statistic	P Value	Crude Odds ratio (95% CI)
	Increase	Decrease			
<b>Diabetes</b>					
Yes	74 (72.5)	17 (37.0)	3.989	<0.01	4.5 (2.2, 9.6)
No	28 (27.5)	29 (63.0)			
<b>Gender</b>			0.650	0.515	1.26 (0.63, 2.58)
Female	48 (47.1)	19 (41.3)			Reference
Male	54 (52.9)	27 (58.7)			
<b>Smoking</b>			-0.991	0.322	0.56 (0.19, 1.82)
Yes	8 (7.8)	6 (13.0)			Reference
No	94 (92.2)	40 (87.0)			
<b>BMI (kg/m<sup>2</sup>)</b>			22.7	<0.01	Reference
Normal (18.5 – 22.9)	16 (15.7)	10 (21.7)			2.40 (0.34, 20.77)
Underweight (<18.5)	2 (2.0)	3 (6.5)			
Overweight (23.0 – 24.9)	14 (13.7)	8 (17.4)	0.877	0.380	2.63 (0.36, 23.37)
Obese 1 (25.0 – 29.9)	41 (40.2)	16 (34.8)	0.951	0.342	
Obese 2 (>30.0)	29 (28.4)	9 (19.6)	1.404	0.160	3.84 (0.59, 31.31)
			1.592	0.111	4.83 (0.70, 41.37)
<b>IHD</b>			1.53	0.125	1.98 (0.86, 5.01)
Yes	30 (29.4)	8 (17.4)			Reference
No	72 (70.6)	38 (82.6)			
<b>Gout</b>			-0.600	0.549	0.70 (0.22, 2.43)
Yes	8 (7.8)	5 (10.9)			Reference
No	94 (92.2)	41 (89.1)			
<b>Hyperlipidaemia</b>			0.999	0.318	1.43 (0.71, 2.89)
Yes	60 (58.8)	23 (50.0)			Reference
No	42 (41.2)	23 (50.0)			
<b>Stroke</b>			0.147	0.883	1.13 (0.23, 8.13)
Yes	5 (4.9)	2 (4.3)			Reference
No	97 (95.1)	44 (95.7)			
<b>Hypertension</b>			0.0808	0.419	2.27 (0.27, 19.43)
Yes	100 (98.0)	44 (95.7)			Reference
No	2 (2.0)	2 (4.3)			
	<b>Mean (SD)</b>				
Age (years)	56.6 (12.0)	49.2 (10.2)	3.383	<0.01	1.06 (1.03, 1.10)
Duration HD (years)	3.9 (3.1)	4.5 (3.4)	-0.983	0.326	0.95 (0.86, 1.06)
BMI (kg/m <sup>2</sup> )	27.3 (5.1)	25.6 (5.8)	1.756	0.079	1.06 (0.99, 1.14)
HbA1c (%)	6.9 (1.6)	6.1 (1.5)	2.613	<0.01	1.44 (1.12, 1.94)
HSCRP (mg/L)	8.4 (8.3)	6.4 (6.1)	1.42	0.155	1.04 (0.99, 1.10)
Ferritin (µg/L)	622.2 (413.1)	560.2 (421.7)	0.807	0.412	1.00 (0.99, 1.00)
Albumin (mmol/L)	38.5 (4.0)	39.9 (3.0)	-2.109	0.035	0.89 (0.80, 9.88)
Clearance (%)	69.5 (9.0)	69.0 (9.4)	0.260	0.795	1.01 (0.97, 1.05)
LDL (mmol/L)	3.0 (1.2)	3.0 (1.0)	0.115	0.908	1.02 (0.75, 1.39)
HDL (mmol/L)	0.99 (0.2)	1.0 (0.3)	-1.174	0.240	0.44 (0.11, 1.74)
HB (g/dL)	10.44 (1.7)	10.40 (1.7)	0.168	0.866	1.02 (0.83, 1.25)
TG (mmol/L)	2.3 (1.8)	1.9 (1.1)	1.334	0.182	1.20 (0.94, 1.61)
Transferrin saturation	24.0 (10.2)	25.2 (10.9)	-0.611	0.541	0.99 (0.96, 1.02)
Calcium (mmol/L)	2.17 (0.21)	2.16 (0.24)	0.336	0.737	1.31 (0.26, 6.34)
Phosphate (mmol/L)	1.9 (0.6)	2.1 (0.7)	-1.408	0.160	0.68 (0.39, 1.16)
ALP (U/L)	148.6 (108.0)	175.0 (154.4)	-1.169	0.242	0.99 (0.99, 1.00)
iPTH (pmol/L)	78.1 (67.6)	100.5 (102.4)	-1.465	0.162	0.99 (0.99, 1.00)

Table 3 shows simple logistic regression analysis of sociodemographic, clinical co-morbidities and blood parameters among patients in cohort (n=148) with post hemodialysis hyperglycemia (PHH). Diabetes, Body Mass Index (BMI) category, Ischemic Heart Disease (IHD), age, glycated hemoglobin (HbA1c), highly sensitive C-reactive protein (hs-CRP) and albumin were significant at P<0.15 to be included in multiple logistic regression.

**Table 4.** Multiple logistic regression analysis for factors associated with post hemodialysis hyperglycemia (PHH) (N=148)

Variable	β	SE	Wald	Adjusted OR (95% CI)	P-Value
<b>Diabetes</b>	<b>1.08</b>	<b>0.56</b>	<b>1.951</b>	<b>2.96 (1.01, 9.09)</b>	<b>0.050*</b>
<b>Age (years)</b>	<b>0.041</b>	<b>0.019</b>	<b>2.157</b>	<b>1.04 (1.00, 1.08)</b>	<b>0.031*</b>
IHD	0.584	0.515	1.134	1.80 (0.68, 5.22)	0.257
HBA1c (%)	0.004	0.176	0.026	1.00 (0.72, 1.44)	0.980
Albumin (mmol/L)	-0.093	0.065	-1.429	0.91 (0.80, 1.03)	0.153
HSCRP (mg/L)	0.0152	0.031	0.497	1.02 (0.96, 1.08)	0.620
<b>BMI (kg/m<sup>2</sup>)</b>				Reference	
Normal (Reference)	-	-	-	Reference	
Underweight	0.588	1.05	0.558	1.80 (0.22, 16.89)	0.577
Overweight	0.023	1.10	0.021	1.02 (0.12, 10.28)	0.983
Obese	0.643	1.02	0.628	1.90 (0.25, 16.94)	0.530
Obese Class 1	1.12	1.06	1.051	3.06 (0.38, 29.24)	0.293

Table 4 shows multiple logistic regression analysis of significant factors associated with post hemodialysis hyperglycemia among ESRD patients during hemodialysis (HD) day. OR, odd ratio; HbA1c, glycated hemoglobin; HSCRP, highly sensitive C-reactive protein; Ischemic Heart Disease (IHD) and BMI class. R<sup>2</sup>= 0.258 (Nagelkerke) \*P<0.05.

albumin were associated with the risk of PHH. Table 4 shows the final multivariate logistic regression model, the model is fit with R<sup>2</sup> of 0.258. Increasing age of the

patient are significant with adjusted odds ratio of 1.04, while DM-ESRD had adjusted odds ratio of almost three times higher than NDM-ESRD.

## DISCUSSION

Cardiovascular disease is the leading cause of morbidity and mortality in ESRD particularly in diabetic patients, where the excessive cardiovascular risk may be attributed to underlying co-morbidities and population-based factors; however, these do not account for all the observed risk.<sup>4</sup> Studies have shown that besides the average HbA1c (a marker for chronic hyperglycemia), short-term glycemic variation (GV) is also an independent risk factors for diabetic complications.<sup>12-14</sup> GV, which describes glycemic fluctuations or oscillations around a mean value, is an independent risk factor for diabetes-associated morbidity and mortality.<sup>15</sup> Post-prandial hyperglycemia; among the main contributors to GV, similar to PHH, was shown to play a significant role in the pathophysiology of diabetic complications in terms of inducing oxidative stress and the inflammatory process.<sup>16,17</sup> Hence, it is crucial to evaluate the glycemic pattern in hemodialysis patients, especially emphasizing PHH, as it is one of the main contributors to glycemic fluctuations.

In our study, DM-ESRD patients had more significant glycemic fluctuations compared to those with NDM-ESRD. During hemodialysis days, we observed that PHH was fourfold higher in DM-ESRD compared to NDM-ESRD patients. An 80% rise in blood glucose post-hemodialysis occurred in 82% of diabetic patients. This hyperglycaemia was subsequently persistent throughout the day. On the other hand, this persistent hyperglycemia post hemodialysis was not seen among NDM-ESRD patients. This shows that hemodialysis predisposes DM-ESRD patients to constant hyperglycemia. Other patients exhibited lowered blood glucose levels in the first hour of hemodialysis, which subsequently became constant over the four hours of hemodialysis. This asymptomatic intradialytic hypoglycemia was observed in 18 (12.6%) patients, and more markedly seen in NDM-ESRD patients i.e., 11 (19.3%) patients. In the DM-ESRD patients, only 7 (7.8%) of out of the 91 patients developed intradialytic hypoglycemia; and the majority occurred in the first hour of hemodialysis with a mean blood glucose pre-hemodialysis of 5.4 mmol/L. Most of these patients were on insulin treatment. Although patients with NDM-ESRD had no significant glycemic fluctuations during hemodialysis, almost half experienced a reduction in blood sugar levels post-hemodialysis. Development of intra-dialytic hypoglycemia and reduction of blood sugar among ESRD patients even non-diabetic was an important observation, as currently there are no guidelines on management of insulin or OHA on hemodialysis days, which is left to the nephrologist's discretion.<sup>7</sup> However, we demonstrated that the number of patients developing intra-dialytic hypoglycemia was small compared to those developing PHH, which is similar to previous studies.<sup>18-20</sup> Furthermore, among our population, all patients were encouraged to eat during hemodialysis to prevent episodes of hypoglycemia.

Our observations were similar to other studies on hemodialysis patients. Abe et al. showed that plasma glucose decreased with hemodialysis and hyperglycemic spikes were observed post hemodialysis which were attributed to decreased insulin due to hemodialysis clearance and/or the release of counter-regulatory hormones.<sup>6</sup> Similar intradialytic glucose reduction and

PHH were observed by Gai et al., which demonstrates PHH occurs 150 minutes post-hemodialysis.<sup>20</sup> Kazempour-Ardenilli et al., showed glycemic readings were lower on hemodialysis days as compared to non-hemodialysis days.<sup>18</sup> Both Mirani et al., and Jin et al., showed that GV was more pronounced on hemodialysis days, however, mean blood glucose was lower on hemodialysis days compared to non-hemodialysis days.<sup>11,19</sup>

This observation of intra-dialytic hypoglycemia coupled with significant PHH should prompt the nephrologist to adjust glycemic management of DM-ESRD patients. Possible administration of additional insulin or less hypoglycemic agents e.g., dipeptidyl-peptidase 4 inhibitors or glucagon-like-peptide analogs post-hemodialysis or on hemodialysis days will eventually help reduce glycemic fluctuations.<sup>6,21-23</sup> Development of intradialytic hypoglycemia should be taken seriously because, as shown in our study and previous studies, a majority of these events were asymptomatic (role of autonomic neuropathy in long-standing diabetes).<sup>5,24</sup> Events of intradialytic hypoglycemia were mostly asymptomatic in our study and previous studies, suggesting underlying autonomic neuropathy from long-standing diabetes. These might suggest the possibility of other undetected hypoglycemic events which may further aggravate glycemic fluctuations. Therefore, the role of additional intra-dialytic glucose monitoring should be further studied.

In our study, we report that PHH, as reported by SMBG, is more significant in patients with DM-ESRD, older age, obesity and previous IHD. Other associated blood parameters include high HbA1c, elevated hs-CRP and lower albumin. The association between HbA1c levels and glycemic fluctuations and mean blood glucose had been heavily investigated previously with conflicting results. Conversely, studies have shown that HbA1c has a weak correlation with glycemic fluctuations but has a significant relationship with chronic hyperglycemia and mean blood glucose.<sup>25-28</sup> Interestingly, recent studies among Asian populations showed similar findings to our study where HbA1c correlates with glycemic variability indices.<sup>29,30</sup> Notably, most of these studies exclude ESRD patients where HbA1c is a less reliable surrogate for glycemic control as it may falsely increase or decrease due to factors related to ESRD, e.g. anemia and uremia.<sup>7,31</sup> Anemia present in 42% of our population may have confounded our findings of 68% of patients with HbA1c less than 8%, with mean of 7.4% (reasonable control). The correlation between mean blood glucose and HbA1c in our population was moderate with  $R^2$  of 0.59, similar to other studies on DM-ESRD where the  $R^2$  is not more than 0.50 compared to NDM-ESRD with  $R^2$  more than 0.80.<sup>27,32</sup> Nonetheless, HbA1c level more than 8.5% in DM-ESRD patients was related to increased mortality and should not deter clinicians from controlling the glucose level.<sup>31</sup>

PHH is also associated with older age in which there is pancreatic beta cell dysfunction with limited capability to generate coupled with insulin resistance.<sup>33,34</sup> Studies have shown that beta-cell dysfunction plays a significant role in explaining dysglycemia, where insufficient insulin secretion for accurate glycemic regulation may lead to glucose-related metabolic disorders, resulting in increase glucose fluctuations and sustained hyperglycemia.<sup>35,36</sup> Other studies

also showed similar findings where glucose fluctuations are more marked in the older age population.<sup>29,30</sup>

Previous IHD, high hs-CRP along with low albumin and relative obesity can be explained by the malnutrition-inflammatory complex syndrome (MCIS), which a term coined to describe the chronic inflammatory state in hemodialysis patients, which is usually accompanied by malnutrition or protein-energy wasting (PEW).<sup>5</sup> Oxidative stress and high inflammatory levels are associated with endothelial dysfunction and subsequently, micro and macro-angiopathy in diabetic patients, particularly resulting in cardiovascular complications.<sup>37</sup>

We specifically looked at the inflammatory biomarker hs-CRP to add prognostic information on cardiovascular risk in our population. A previous study evaluated the role of hs-CRP and showed that there was a linear relationship with vascular risk; a value of less than 1mg/L (lower risk), 1 to 3 mg/L (moderate risk) and more than 3mg/L (higher risk).<sup>38</sup> In hemodialysis patients, although elevated hs-CRP at a single time point is an important predictor of cardiovascular events, the values are not static and may reflect the chronic inflammatory process due to hemodialysis, intercurrent clinical events, decreased residual renal functions and PEW.<sup>39-41</sup> A study done in hemodialysis patients showed that serum CRP levels increased annually during the follow up period.<sup>42</sup> In our study, the mean hs-CRP in DM-ESRD and NDM-ESRD patients were 8.91 mg/L and 7.03 mg/L respectively, with only 41 (27.7%) of patients with level less 3 mg/L. This suggests that hemodialysis patients, regardless of their diabetic status, were in a constant state of inflammation, which predisposes them to a higher risk of a cardiovascular event. PEW, on the other hand, represented by low albumin, is common among patients undergoing maintenance hemodialysis and is by far the strongest risk factor for adverse outcomes and death.<sup>43</sup>

A 10-year cohort study which evaluated serum albumin, C-reactive protein, and carotid atherosclerosis as predictors of 10-year mortality in hemodialysis patients showed that serum albumin concentration was superior as a predictor of mortality.<sup>44</sup> However, in our cohort, the difference between 38 mmol/L among patients experiencing PHH compared to 40 mmol/L maybe hard to appreciate in clinical setting. Nonetheless, by addressing the issue of malnutrition and chronic inflammation among hemodialysis patients, we may improve the occurrence of glycemic fluctuations and subsequently improve outcomes in these patients.

The first limitation of this study was its cross-sectional design and one-off blood sugar monitoring during hemodialysis and non-hemodialysis days. This design may not accurately represent the overall picture of the patients, as many factors can influence single snapshot monitoring. Another limitation was the usage of SMBG instead of continuous glucose monitoring system (CGMS) in assessing PHH. CGMS is preferable as SMBG can miss specific peaks and nadirs in glucose values.<sup>45,46</sup> However, it is challenging to perform CGM in daily practice, given discomfort, cost, and the need for calibration compared to the SMBG. The practical aspect of SMBG in terms of easy availability, monitoring and interpretation, and lower cost makes it the preferred method in our population. We did not limit or measure dietary intake of patients during the

study period, which makes it an additional confounding factor in the glycemic profile of the patients. Some previous studies restricted dietary intake or asked the patient to fast during hemodialysis to reduce confounding. However, doing so is not reflective of the normal day-to-day glucose fluctuations of patients, and allowing normal dietary intake reflects real-life data and consequently will allow meaningful alterations in management.

## CONCLUSION

DM-ESRD patients experienced more significant fluctuations of glucose level, in particular, PHH on hemodialysis day compared to those with NDM-ESRD. Other associated factors for PHH include older age group, previous IHD, obese patient, high HbA1c, and hs-CRP coupled with low albumin. Malnutrition-inflammatory-complex syndrome, together with protein-energy wasting commonly seen among chronic hemodialysis patients, should be cornerstones in managing this group of patients as improving this phenomenon may improve glucose control and subsequently improve diabetes-related complications and mortality. Regular glucose monitoring via SMBG may provide valuable insights for treating physicians among this high-risk group.

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## Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

## Author Disclosure

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