

A Case of Burnt out Diabetes in an End Stage Renal Disease Patient at a Private Multispeciality Tertiary Care Hospital

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ABSTRACT

Burnt-out diabetes is a state in which diabetic patients with End Stage Renal Disease (ESRD) experience hypoglycemic episodes accompanied by a normalization of Glycosylated Hemoglobin A1c (HbA_{1c}) levels. Here we present a case of 'burnt-out diabetes' in a female patient who went into sudden cardiac arrest during hemodialysis. Patient reverted and after intubation was admitted under intensive care. Investigations revealed severe Chronic Renal Failure (CRF), mild concentric left ventricular hypertrophy (LVH) and mild pulmonary arterial hypertension (PAH). She was treated with intravenous antibiotics, diuretics, antihypertensives. She had four sittings of hemodialysis during her hospital stay and was later discharged and advised regular hemodialysis. In conclusion, this is a case that involves interplay of diabetes and kidney disease. This emphasizes the need to evaluate the risks associated with the overestimation of glycemic control in ESRD patients on hemodialysis and for the use of alternative indicators of glycemic control such as Glycated Albumin (GA).

Key words: Diabetes mellitus, Glycosylated hemoglobin, Hemodialysis, Glycemic control, Glycated albumin.

INTRODUCTION

Type 2 Diabetes mellitus is one among the most common causes for the development of chronic kidney disease (CKD).¹ Traditionally, measure of glycemic control is evaluated on the basis of Glycosylated Hemoglobin (HbA_{1c}) levels. It can be defined as the glycated percentage of total hemoglobin (Hb) and indicates control over a period of time (3 months).² The target for glycemic control in diabetic patients without renal disease is an HbA_{1c} level less than 6.5% or 7%.³

A glomerular filtration rate (GFR) below 60 ml/min/1.73 m² for a period longer than 3 months has been defined as CKD.⁴ Nearly 35 to 45% of diabetic patients develop nephropathy. This complication has been associated with the highest mortality among others such as retinopathy and neuropathy. Within a period of 5 years, these patients usually develop hypertension. Within the next 5-10 years, they are observed to develop

nephrotic syndrome, marked by a gradual reduction in the GFR, ultimately leading to End Stage Renal Disease (ESRD). For such patients who eventually develop ESRD, dialysis and transplantation are the treatment options.⁵

In about one-third of the diabetic population undergoing dialysis, it has been reported that spontaneous normalization of HbA_{1c} (below 6%) accompanies the progression of CKD. This sequence of clinical events results in a phenomenon commonly known as 'Burnt-out diabetes'. This subsequently results in the discontinuation of insulin and other anti-diabetic drugs.²

CASE REPORT

A 64 year old female patient was presented for admission at Sri Ramakrishna Hospital, Coimbatore with a medical history of systemic hypertension (since 2 years), diabetes mellitus (since 10 years), coronary

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artery disease (since 1 year), ESRD on hemodialysis (since past 1 year) underwent sudden cardiac arrest during hemodialysis. Cardiopulmonary resuscitation (CPR) was initiated as per advanced cardiac life support protocol. The patient was reverted, intubated and admitted under intensive care. She had history of a similar episode of cardiac arrest during hemodialysis a month ago. CPR was performed and the patient was unconscious for two days. On regaining consciousness, she was restless but responded to painful stimuli and was on endotracheal tube. She was found to be anemic and hence blood transfusion was performed and discharged.

During the current course of admission, she was drowsy, responded to painful stimuli and had a blood pressure of 210/180 mmHg. Investigations were performed, which revealed severe chronic renal failure (serum creatinine: 5.7 mg/dl, estimated glomerular filtration rate (eGFR): 7 ml/min/1.73m²), anemia (hemoglobin: 8.2 g/dl), a HbA_{1c} value of 5.2% and an elevated whole blood D Dimer level of 4070 mcg/L. During the course of hospital stay, the patient was observed to have recurrent episodes of hypoglycemia and a fluctuating blood glucose profile in summation. In view of recent episode of cardiac arrest, holter monitoring was done, which was normal. Cardiac assessment was performed and echocardiography showed mild concentric Left Ventricular Hypertrophy (LVH) and mild pulmonary arterial hypertension (PAH). A coronary angiogram was performed, which showed significant single vessel disease.

Patient was treated with intravenous antibiotics (piperacillin/tazobactam 4.5gm bd), intravenous diuretics (furosemide 20mg bd), oral antihypertensives (nebivolol 2.5mg od, cilnidipine 10mg od), nebulization (levosalbutamol/ipratropium bromide) and her usual medications for pre-existing conditions. The patient had four sittings of hemodialysis during the hospital stay after which she was discharged and advised regular hemodialysis.

DISCUSSION

The patient is a known case of diabetes since 10 years but was not on any diabetic medication since one year. Her investigations revealed anemia, fluctuating blood glucose levels (Figure 1), a normoglycemic HbA_{1c} and ESRD. Her current clinical features are suggestive of the 'Burnt-out diabetes' phenomenon.

Generally, an optimal glycemic control is associated with a lower incidence of cardiovascular events and all-cause mortality in the Type 2 diabetes population.⁶ However, in diabetic patients with ESRD undergoing hemodialysis

(HD), a normoglycemic HbA_{1c} (5 to 5.9%) is often noted. Such overestimation of glycemic control may contribute to higher mortality rates.⁷

Unusual fluctuations in glycemic control have been noted in diabetic patients undergoing dialysis.⁸ In case of patients with End Stage Renal Disease (ESRD), there are multiple confounding factors that influence HbA_{1c}, often resulting in a lower or higher A1c level in patients undergoing dialysis.²

In most patients with CKD, the lifespan of erythrocytes is reduced by nearly 30-70%.⁹⁻¹¹ Due to a reduction in the survival of red blood cells (RBC), there is a subsequent decline in the duration of exposure to blood glucose, thereby reducing the degree of glycation leading to lowered HbA_{1c} levels.¹² ESRD patients also present with anemia, which is managed by erythropoietin stimulants and blood transfusion when necessary. Due to this, there is an increase in the circulation of immature erythrocytes accompanied by a lesser likelihood of glycation of the newly formed erythrocytes, leading to normoglycemic range of HbA_{1c}.^{13,14}

Due to this variation in HbA_{1c} observed in patients with ESRD and those who are continually undergoing dialysis, it implies that HbA_{1c} level may provide an overestimation of the degree of glycemic control in CKD patients result in burnt-out diabetes.⁸

Generally, it is interpreted that lower A1c levels indicate excellent glucose control, thereby proving to be advantageous. However, as far as patients with burnt-out diabetes are concerned, there is a higher risk of mortality and morbidity due to sudden increase and decrease of glycemic levels.¹⁵

Interestingly, in ESRD patients undergoing treatment with erythropoietin, HbA_{1c} levels were found to reduce.

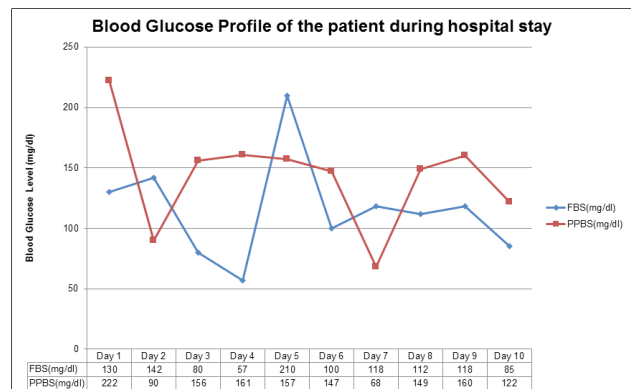


Figure 1: Blood glucose profile of the patient during hospital stay.

But, when the treatment was stopped, it was noted to increase.¹⁶ Erythropoietin is known to stimulate the production of newer RBCs. Since HbA_{1c} is the measure of the total hemoglobin that undergoes glycation, the extent of glycation of newly produced RBCs is lower than that of mature older RBCs. The decrease in HbA_{1c} levels in such patients can therefore be correlated to an increased number of circulating young RBCs due to erythropoietin treatment.¹³

Another study performed in CKD patients undergoing hemodialysis noted that anemia (due to reduced Hb levels) would lead to reduced HbA_{1c} levels. However, stopping treatment with erythropoietin increased HbA_{1c} and reduced Hb instead of decreasing both.¹⁶ Such a controversial relationship between Hb and HbA_{1c} may suggest that HbA_{1c} may not be the most reliable indicator of glycemic control in diabetic patients undergoing hemodialysis and receiving erythropoietin treatment, as it involves a false reduction of HbA_{1c} values.¹⁷

Therefore, there is a need for an alternative and accurate indicator of glycemic control in patients with ESRD undergoing hemodialysis, as HbA_{1c} is influenced by factors such as RBC lifespan, anemia, frequent dialysis and erythropoietin treatment.¹⁸

Since the validity and accuracy of the standard HbA_{1c} test is influenced by such clinical scenarios, several non-traditional markers of glycemic control have emerged, such as fructosamine, glycated albumin and 1,5-anhydroglucitol (1,5-AG) to quote a few.

A fructosamine assay reflects the mean blood glucose levels over the previous two to three weeks, indicating recent glycemic fluctuations. However, the assay is limited by a high degree of within-subject variability which may necessitate frequent measurements.

1,5-AG has a better clinical utility in scrutinizing the glycemic control in type 1 diabetes patients. However, it is influenced by alterations in renal hemodynamics.¹⁹

Glycated Albumin (GA) measures the glycation product of albumin and can provide a suitable alternative for indicating the extent of glycemic control over a shorter duration of time. In comparison to hemoglobin, plasma albumin has a shorter half-life (15 to 20 days), thereby enabling a much more rapid detection of glycemic changes. This is particularly beneficial for patients with fluctuating glucose levels and those facing recurrent episodes of hypoglycemia.²⁰ The glycation speed of albumin and hemoglobin were compared and it was

found that albumin is ten times faster than hemoglobin. Therefore, rapidly fluctuating glycemic control is reflected at a faster rate on albumin than hemoglobin. Since HbA_{1c} reflects mean glucose levels over a period of two to three months, the response observed is much slower.¹⁹

Particularly in diabetic patients with CKD, GA has been suggested as a more reliable indicator that is more sensitive to glycemic changes than HbA_{1c}, as it is unaffected by anemia and erythropoietin treatment.²¹ Previous studies indicate that GA can be employed as a reliable marker of glycemic control in diabetic patients with anemia, as HbA_{1c} was observed to provide misleading results about glycemic control.²²

GA was also observed to be associated with vascular outcomes and mortality that was comparable to those observed with HbA_{1c}.²³ Studies have found a better association between GA levels and the prediction of development of diabetic nephropathy in both type 1 and 2 diabetic populations.²⁴

A meta-analysis showed that in early stages of CKD, statistically significant differences were not observed between GA and HbA_{1c}. However GA was found to be superior to HbA_{1c} in patients with advanced CKD. It was also noted that increased GA levels were associated with the presence and severity of CV disease and deranged kidney function. GA can thereby serve as an efficient predictor of vascular complications associated with diabetes (microvascular and macrovascular) and a reliable indicator of glycemic control in the diabetic CKD population.¹⁷

CONCLUSION

This case of burnt-out diabetes phenomenon highlights the discrepancies of using HbA_{1c} as the standard for assessing glycemic control in special populations such as diabetic patients undergoing hemodialysis. HbA_{1c} is greatly influenced by anemia, RBC lifespan, frequent dialysis and erythropoietin treatment in patients with advanced CKD, thereby overestimating the glycemic control in such populations by showing false reductions. There is a need for a more reliable and sensitive indicator of glycemic control such as GA, which is not influenced by variables affecting HbA_{1c}. Additionally, GA also helps in the prediction of developing vascular complications in patients with diabetic nephropathy. Further studies specific to the Indian population are necessary to examine and establish the scope of utilizing GA over HbA_{1c} in HD patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ESRD: End Stage Renal Disease; **HbA1c:** Glycosylated hemoglobin A1c; **CRF:** Chronic Renal Failure; **LVH:** Left Ventricular Hypertrophy; **PAH:** Pulmonary Arterial Hypertension; **GA:** Glycated Albumin; **CKD:** Chronic Kidney Disease; **GFR:** Glomerular Filtration Rate; **CPR:** Cardiopulmonary Resuscitation; **Hb:** Haemoglobin; **eGFR:** Estimated Glomerular Filtration Rate; **HD:** Hemodialysis; **RBC:** Red Blood Cells; **1,5-AG:** 1,5-Anhydroglucitol; **FBS:** Fasting Blood Sugar; **PPBS:** Post Prandial Blood Sugar.

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