

GLYCEMIC STATUS IN DIABETIC AND NON-DIABETIC ESRD PATIENTS WITH OR WITHOUT HEMODIALYSIS IN RURAL HOSPITAL OF CENTRAL MAHARASHTRA

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ABSTRACT

Background: Diabetes is a potent cardiovascular risk factor in the general population as well as in people with end-stage renal disease (ESRD) undergoing maintenance dialysis treatment. Previous observational studies have yielded inconsistent results regarding the association between glycemic controls in patients receiving maintenance hemodialysis (MHD). Studies provide evidence that very poor glycemic control is associated with higher mortality in dialysis patients. The significance of the levels of glycosylated haemoglobin in non-diabetic patients with renal disease receiving maintenance hemodialysis remains unclear at the present time. The knowledge of HbA1c in patients with renal diseases could be important in assessing the overall prognosis in such patients and it also has implications in the assessment of their glycaemic status and in preventing post-dialysis morbidity and mortality.

Aims & Objective: (1) To study the role of HbA1c as a marker of glycemic status in patients of kidney disease with or without MHD. (2) To compare the utility of fasting glucose level and HbA1c in accessing glycemic status and their relationship.

Material and Methods: Study was conducted in the AVBRH, Jawaharlal Nehru medical college, Sawangi (M) Wardha by department of Biochemistry in collaboration with Department of Medicine. 30 patients undergoing maintenance hemodialysis and 30 patients of kidney diseases who are not undergoing MHD, has been taken from AVBRH Sawngi (Meghe). 30 age and sex matched healthy controls were also included in the study. 5.0 ml of blood has been collected from each subject after informed consent. Different parameters such as HbA1c, Fasting and random blood glucose, Urea creatinine, sodium potassium were evaluated in all the groups.

Results: Study concluded that the HbA1c values in CKD patients undergoing hemodialysis is found above the normal range (6.71 ± 0.99) as compared to the control group (4.38 ± 0.52) while the results of HbA1c in CKD patients not going through hemodialysis found to be within the normal range (4.93 ± 0.52) and less than the patients going through the hemodialysis (6.71 ± 0.99) but more than the control group (4.38 ± 0.52).

Conclusion: In non-diabetic patients with ESRD undergoing hemodialysis HbA1c may be used as a marker of impaired glucose metabolism and glycemic control is necessary to prevent future complications in these patients. Secondly in CKD patients not undergoing hemodialysis HbA1c value are more than control though they are under normal limit but it should be strictly monitored.

Key-Words: Hemodialysis; End Stage Renal Disease; Diabetes; HbA1c; Hyperglycaemia

Introduction

Advance in the medical technology and improvement in public health have brought a progressive increase in the population undergoing hemodialysis (HD).^[1] Hemodialysis is a form of treatment where accumulated solute and fluid are removed from a patient who has total or near total loss of kidney function using hemodialysis machines which utilize extracorporeal blood lines and artificial kidney called dialyzer. It is indicated for acute kidney injury, acute exacerbation of chronic renal failure and end stage renal diseases (ESRD). It is most commonly use modality of renal replacement therapy worldwide.^[2] Over 1.1 million patients are estimated to have renal failure worldwide with an annual increase at a rate of 7%. In developing countries the growth of CRF population has similar trends.^[3] Chronic Kidney disease (CKD) is a global threat to health in general and for developing countries in particular, because therapy is expensive and lifelong. In

India nearly 90% patient cannot afford the cost. Over 1 million people worldwide are alive on dialysis or with a functioning graft. Incidence of CKD has doubled in the last 15 years.^[4]

According to World Health report 2002 and Global Burden of Disease (GBD) Project, diseases of the kidney and urinary tract contribute to the global burden of disease, with approximately 850000 deaths every year and 15010167 disability-adjusted life years. They are 12th cause of death and 17th cause of disability respectively.^[5]

There is wide variation in prevalence rate, expressed as number of patients per million populations among countries. Although there is lack of uniform data around the world, the total number of those who need RRT is growing in all high income countries and also in middle income countries.^[5] According to European Renal Association European Dialysis and Transplant Association (ERA_EDTA) registry reports an 18% first year mortality

rate, whereas the US Renal Data System reports even higher annual mortality of 20%.^[6]

ESRD incidence data are not available from large parts of the developing world including South Asia. One study reported the ESRD incidence in large urban population in India and average crude and age adjusted incidence rates were found to be 151 and 232 per million population respectively. The mean age was 47 years and 58% were male. The population of India exceeds one billion and is projected to become the major reservoir of chronic diseases like diabetes and hypertension. With 25-40% of these likely to develop CKD, the ESRD burden will rise and health care system would need to take care of these individual.^[7] The overall prevalence of CRF in India is nearly 0.8% in India.^[4] Kidney disease ranked 3rd amongst life threatening disease in India after cancer and heart disease. About 200000 people go into terminal kidney failure every year.^[8]

Considering the etiological cause of the CRF diabetes is the most common cause followed by hypertension.^[4,7,9,10] Sakhuja et al reported an estimated annual incidence of ESRD in India and Pakistan at <100 per million population, which appears to be lower than the 98–198 per million reported from ESRD registries of developed countries. The incidence of ESRD in India would be expected to be higher since poor socioeconomic status predisposes the population to a number of infection-related glomerulonephritis and the incidence of nephrolithiasis is higher in both countries as they fall in a “stone belt”.^[11]

Diabetic patients have higher co morbidity and poorer outcome compared with non-diabetic patients on dialysis as reflected by a 5 year survival only 35%. Poor glycemic control is associated with the development of co morbidities such as coronary arteries disease and myocardial infarction in the general population. Furthermore glycemia is known to influence the electrolyte balance, the function of potassium and calcium channels, the sympathetic activity, all relevant in the arrhythmogenesis of patients with kidney failure. Therefore glycemic control is necessary in diabetic as well as nondiabetic patients undergoing hemodialysis.^[6]

The Diabetes Control and Complication Trial (DCCT) and UK Prospective Diabetes study (UKPDS) showed that monitoring blood glucose at normal or near normal levels can reduce the incidence of micro vascular complications in patients with type 1 & 2 diabetes respectively.^[10,12-14] A significant percentage of patients have ESRD, however and poor glycemic control has been shown to be a predictor of mortality in diabetic patients starting dialysis.^[12]

Atherosclerotic vascular disease also the most frequent complication in patients undergoing chronic hemodialysis treatment and can be a cause of mortality in these patients^[15] and these events may occur at an accelerated rate if glycemic control is not there. Some studies also focused their attention to non-diabetic patients as inconsistent results are there in non-diabetic patients undergoing hemodialysis and data is very sparse. Reduced kidney function is now recognized as a powerful and independent risk factor for CVD morbidity and mortality. Disorders of glucose homeostasis are common in CKD. Two studies using data from the Third National Health and Nutrition Examination Survey found a high prevalence of impaired fasting glucose levels (defined as <110 mg/dl) among individuals with reduced GFR and those with microalbuminuria.^[16]

Glycated haemoglobin (HbA1c) level, which indicates the percentage of circulating haemoglobin that has chemically reacted with glucose, reflects the blood glucose level over the 120 days preceding the test; glucose levels during the 30 days before the test have the biggest impact on HbA1c level. The lack of specific guidelines for assessing glycemic control in patients who are receiving hemodialysis has resulted in the HbA1c assay which is widely used in the general population being the test of choice in this setting.^[13] It has been reported that strict glycemic control, as indicated by lower glycated haemoglobin (HbA1c) levels, has beneficial effects on the prognosis of patients who have diabetes with chronic kidney disease and undergo regular hemodialysis.^[17]

With this background we have hypothesized that strict glycemic control which is not only necessary in diabetic ESRD patients undergoing hemodialysis but also very necessary in non-diabetic CKD patients not undergoing hemodialysis to prevent microangiopathic complications and to improve survival in ESRD patients. HbA1c can be a good marker in this condition so we have evaluated the HbA1c level in CKD patients with and without hemodialysis in our clinical setting.

Aim & Objectives: (1) To study the role of HbA1c as a marker of glycemic status in patients of kidney disease with or without MHD. (2) To compare the utility of fasting glucose level and HbA1c in accessing glycemic status and their relationship.

Materials and Methods

This study was conducted with permission of institutional Ethical committee at Acharya Vinoba Bhave Rural Hospital,

Department of Biochemistry, Jawaharlal Nehru Medical College, Sawangi (M) Wardha in collaboration of Department of Medicine. Verbal consent was obtained for performing tests on the patient's serum sample.

The patients are divided into following groups: (i) **Group-1:** 30 patients from dialysis unit of AVBRH were selected as study group who were undergoing maintenance hemodialysis since 1-4 years. Out of 30 patients 15 were known case of diabetes. (ii) **Group-2:** 30 patients were also taken from AVBRH, Department of Medicine who were suffering from kidney diseases but not undergoing through the maintenance hemodialysis. All were non diabetic. (iii) **Group 3:** The study also included 30 normal healthy adults who served as the control.

The exclusion criteria which were considered were acute cases, pregnancy, active infection, HIV seropositivity. The HbA1c was estimated by immune turbidimetric method using Randox Daytona random access analyzer. HbA1c is presented as A1c/Hb \times 100. The fasting plasma glucose was estimated using GOD-POD based standard kit method with the help of semi auto analyzer. The data were expressed as Mean \pm SD. Students t test was used for statistical analysis and a p value less than 0.05 was considered to be significant.

Results

Table 1 shows the HbA1c values in CKD patients undergoing hemodialysis which is found above the normal range (6.71 ± 0.99) as compared to the control group (4.38 ± 0.52) while the results of HbA1c between CKD patients not going through hemodialysis found to be within the normal range (4.93 ± 0.52) and less than the patients going through the hemodialysis (6.71 ± 0.99) but more than the control group (4.38 ± 0.52).

Table-1: HbA1c and FBS values in Group 1, Group 2 and Control group

	Group 1 (Mean \pm SD)	Group 2 (Mean \pm SD)	Group 3 (Control) (Mean \pm SD)	p value
HbA1c	6.71 \pm 0.99	4.93 \pm 0.52	4.38 \pm 0.52	<0.001
FBS	129 \pm 9.22	112 \pm 4.55	89 \pm 7.23	<0.05

Discussion

Carbohydrate intolerance and impaired glycaemic control is common in ESRD and are thought to be predisposing factors in the development of arteriosclerosis. Many studies have demonstrated the elevated HbA1c levels and deranged glycaemic control in ESRD patients who are on haemodialysis. The mechanism of the elevated HbA1c levels in ESRD patients who received haemodialysis is not clear at the present time. The possibility is that the

patients with ESRD have insulin resistance.^[18] Cross sectional studies in non-diabetic individuals have shown a relationship between HbA1c and prevalent coronary artery disease as well as markers of subclinical atherosclerosis. Population-based prospective studies have also demonstrated an association between HbA1c values in the non-diabetic range and CVD mortality.^[16]

Our study reports deranged HbA1c level in patients undergoing hemodialysis since 1-4 years which also included nearly half of the diabetic known patients. As hyperglycemia play a significant role in the development of microangiopathy, endothelial dysfunction, and impaired myocardial vasodilator function which contribute to cardiac microvessel disease and structural heart disease^[6,12]; these patients are at potential risk.. Josef Zimmermann et al reported that inflammation enhances cardiovascular risk and mortality in hemodialysis patients.^[15] It has been reported that hyperglycemia induce excess generation of highly reactive free radicals, causing oxidative stress, and inflammatory cytokines. In this context, it is important to note that HbA1c is presumably an indicator of a higher load of the Amadori-derived advanced glycation end products, which are known to exert and amplify oxidative stress and can be a consequence of oxidative stress. These Amadori-derived advanced glycation end product toxins are profibrotic and directly involved in the pathogenesis of the inflammatory response syndrome and vascular complications.^[6] Studies also found HbA1c to be a risk factor for all-cause mortality, in general population^[6] and strict glycaemic control at initiation of hemodialysis is an independent predictor of prognosis.^[19] However follow up studies in DM patients for several years on dialysis found that increased risk of mortality for lower HbA1c values, but no associations was found for higher HbA1c levels.^[20] Studies have also indicated that mortality is high if A1C level is > 11% in diabetic dialysis patients or Hba1C level is not at all associated with the mortality in maintenance hemodialysis.^[14] The reason for these conflicting results may be the use of single HbA1c values and time adjusted values may be more useful.

Some guidelines, such as those of the national Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) have recommended that diabetic dialysis patients should follow the American Diabetes Association guidelines^[20] however, there is no consistent evidence to support these recommendation for patients with ESRD. This lack of evidence is highlighted by the KDOQI recommendations, last updated in 2007, stating that target A1C for people with diabetes should be <7% irrespective

of presence of or absence of CKD.^[14]

Tamoaki et al also investigated whether predialysis glycemic control affects the mortality of diabetic patients with ESRD who start hemodialysis treatment and found that better glycemic control is associated with longer survival^[21] and some study suggest that lower glycated haemoglobin levels has beneficial effects on the prognosis of patients who have diabetes with CKD and undergo regular hemodialysis.^[17] In our study when Non Diabetic chronic kidney disease patients are compared with the healthy control, it is observed that the HbA1c level is significantly high(but within the normal range) than the control but significantly low as compared to the hemodialysis patients. Many studies have focused their attention over diabetic patients undergoing hemodialysis and their complications^[6,9,12,14,20] but very few have studied the impact of hemodialysis on non-diabetic individual.^[16,18]

Our study also found the higher HbA1c level in non-diabetic patients undergoing hemodialysis. Many theories have been proposed for high HbA1c in dialysis patients such as insulin resistance, glucose in dialysate, glucose intolerance, etc.^[18] while the precise mechanism still remain obscure. Ramin Sam et al suggested that dialysate should contain adequate amount of glucose because if dextrose is used in dialysate there may be risk of triglyceridemia.^[22]

Studies are there which suggest that chronic hemodialysis increase the risk of atherosclerotic cardiovascular diseases like coronary heart disease, cerebrovascular disease, and peripheral vascular disease^[23] and these events are directly or indirectly related to glycemic status and diabetes; this is further supported by one study of Vinita Elizabeth Mani and colleagues who reported that patients with high HbA1c values have high incidence of acute cardiac states.^[24] Patients with chronic kidney diseases without hemodialysis may later land up into insulin resistance due to result of multitude of factors such as inflammation, oxidative stress, elevated adipokines etc.^[25]

So HbA1c monitoring not only important in diabetic or non-diabetic hemodialysis patients but also in CKD patients without hemodialysis. There are few limitations in this study. First, the follow up of HbA1c measurement was not done in the study cohort which is the further aspect of the future studies along with the correlation of the cardiovascular risk markers traditional; such as lipid profile as well as newer such as Hs CRP and homocysteine level. There is second limitation which can be influencing

that the cause of ESRD were not considered and all the patients who were undergoing maintenance hemodialysis were considered and all the patients with CKD were taken. Factors which can affect the values of HbA1c in ESRD patients such as shortened life span of RBS, anemia, increased proportion of reticulocytes were also not considered however recently used immunomethod for HbA1c estimation suppress these factors up to certain limits. Therefore, we cannot deny a possibility that an independent impact of glycemic control on hemodialysis in CKD patients may be somewhat different.

Conclusion

In Summary, In non-diabetic patients with ESRD undergoing hemodialysis HbA1c may be used as a marker of impaired glucose metabolism and glycemic control is necessary to prevent future complications in these patients. Secondly in CKD patients not undergoing hemodialysis HbA1c value are more than control though they are under normal limit but it should be strictly monitored.

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