Original article:

Glycated Albumin Levels In Non- Diabetic End-Stage Renal Disease Patients Undergoing Haemodialysis

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ABSTRACT

Introduction: Glycated Albumin is recently used as a short term measure for glycaemic control in patients with diabetes mellitus. In this study, an attempt has been made to study glycated albumin levels, which may serve as a reliable indicator of integrated glycaemia in these patients.

Material and Methods: We enrolled 150 non-diabetic end-stage renal disease patients who received haemodialysis and 50 non-diabetic patients without end-stage renal disease for this study. Glycated albumin was analysed by an enzymatic method using albumin specific protease, ketoamine oxidase and albumin assay in order to avoid assay interference from uraemia and anaemia in end-stage renal disease patients.

Results: We found that the average glycated albumin levels in non-diabetic end-stage renal disease patients on haemodialysis was 20.2 ± 2.8% and that in the control group was 12.9 ± 2.1% (p < 0.001). There was no significant difference in the random blood glucose levels between the two groups. Our data indicated that glycated albumin levels are elevated in non-diabetic end-stage renal disease patients undergoing haemodialysis.

Conclusions: We conclude that the elevation in glycated albumin level cannot be solely explained by glucose reabsorption from the dialysis and that it reflects true glucose intolerance. Moreover, correlations between glycated albumin, Glycated hemoglobin and the duration of dialysis. The relation between GA and microalbuminuria also assessed between the groups. It was found that these ratios varied significantly with the increase in GA levels in ESRD patients.

Key words: Glycated albumin, ESRD, haemodiaysis, Macroalbuminuria

Introduction

CKD (chronic kidney disease) is a serious population health problem with a significant impact on individuals, families society and health services.

It is often associated with other complication chronic diseases such as diabetes, hypertension and heart disease. Based on population studies the estimated prevalence of significant kidney impairment (eGFR < 60ml/min) around the world is 1.45,00 people every year approaching the prevalence of Type II diabetes.

However because many cases are undiagnosed this is likely a true significant underestimate (1). There is increase awa-
recess of CKD in all practices. CKD increases the risk of cardiac morbidity and mortality to levels ten times that of population mean risk in addition to placing persons at risk of end stage renal disease requiring dialysis. The levels of HbAlc (glycosylated haemoglobin) reflect the glycaemic control during the erythrocyte life span. So we have drawn attention to the estimate levels of GA in non-diabetic patients who were on intermittent haemodialysis and found significantly higher GA levels but no correlation with blood glucose. The knowledge of GA in patients with ESRD (end-stage renal disease) 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. A multitude of causes leading to increased GA levels have been thought of by various scientists viz; glucose in the dialysates, insulin resistance, glucose intolerance, etc. While the precise mechanisms which cause the elevation of the GA levels remain obscure, this test can be a useful adjunct in the detection of carbohydrate metabolism abnormalities and the consequent CKD risk in these patients.

There are limited reports available on levels of glycated albumin in non-diabetic end-stage renal disease. Therefore this study was planned to assess frequency of GA and the relationship between GA levels, duration of dialysis, in non diabetic end-stage renal disease patients.

Material and Methods

The present cross-sectional study was conducted from December 2010 to December 2012 in MAPIMS&R Hospital, Melmaruvathur, Tamil Nadu respectively. A total of 150 (M: F; 125:25) non diabetic subjects with end-stage renal disease undergoing hemodialysis were selected for this cross sectional study from the dialysis unit, department of Nephrology in MAPIMS&R and were compared with 50 (M: F; 54:26) non diabetic control subjects. After the full explanation of the study, written informed consent was obtained from each study subject. The study was approved by the Ethics committee of the institution prior (EC No. MAPIMS/RC/NOV/2010/44) the informed consent was obtained from all the subjects. Demographic and anthropometric details like age, weight, height, duration of Kidney disease, duration of dialysis were recorded for all the study subjects. Family history of diabetes and hypertension, smoking and alcohol consumption habits were obtained from the medical records of the study subjects.

Purposive random sampling technique was used for data collection. Venous blood samples were collected after 12 hours fasting into two test tubes; with no anticoagulant for serum creatinine, and with anti coagulant for FBG analyzed in Olympus AU 400 auto analyzer. Serum creatinine was analysed by alkaline picrate, Jaffe's Method (Biocon® Kit, Germany) Plasma GA levels were measured by an enzymatic method using albumin specific protease, ketoamine oxidase and albumin assay reagent on the Hitachi Autoanalyser (Lucica GA-L, Asahi Kasei Pharma Corp, Tokyo, Japan). GA was hydrolyzed to amino acids by albumin specific proteinase and then oxidized by ketoamine oxidase to produce hydrogen peroxide, which was measured quantitatively. The GA value was calculated as the percentage of GA relative to total albumin, which was measured with bromocresol purple method. Twenty four hour urine sample was collected in a container (without preservative) for analysis of albumin. Microalbuminuria was estimated by ion-exchange high performance liquid chromatography (HPLC, sigma Aldrich Ascentis® Chennai)
Statistical analysis

The statistical analysis was done by using SPSS version 16.0. One Way ANOVA method was applied to observe association of end-stage renal disease with GA and duration of dialysis. P value ≤ 0.0001 was considered as statistically significant.

Results

There was no significant difference in the average Random blood glucose (RBG) levels between the ESRD and the control groups (p>0.05). However, in non-diabetic control patients, the GA level was 12.9 % ±2.1. In ESRD patients, the GA level was 20.2 % ±2.8. Thus, there was a significant elevation of GA levels in non-diabetic ESRD patients who received haemodialysis (p<0.001).

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<tr>
<th>Table 1 - GA levels in ESRD patients and control group</th>
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<tr>
<td>Parameter</td>
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<tr>
<td>Glucose(mg/dl)</td>
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<td>GA(%)</td>
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ESRD=end stage renal disease

GA=glycated albumin

p-value<0.001 (significant)

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<tr>
<th>Table 2 - GA and Macroalbuminuria Levels in ESRD hemodialysed and Control group</th>
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<tr>
<td>Parameters</td>
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<tr>
<td>GA(%)</td>
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<tr>
<td>Macroalbuminuria(mg/24 hr)</td>
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Macroalbuminuria: F ratio – 67.82, degree of freedom - 1, p value < 0.001.

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<th>Table 3 - GA and HbA1c cardiac risk ratio levels in ESRD hemodialysed and control group</th>
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<tr>
<td>Parameters</td>
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<tr>
<td>GA(%)</td>
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<tr>
<td>HbA1c(%)</td>
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<td>Cardiac risk ratio (TC/HDLc)</td>
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<th>Table 4 - GA levels in ESRD patients according to duration of dialysis</th>
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<td>Duration of Diabetes</td>
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<td>1 year</td>
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<td>2 years</td>
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<td>&lt; 2 years</td>
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P value < 0.001 significant.

Discussion

In this study, we investigated whether the putative renal risk markers macroalbuminuria, impaired renal function, and GA levels can be used for population screening to identify individuals who are at risk for accelerated renal function loss undergoing hemodialysis. Many studies have demonstrated the elevated HbA1c levels and deranged glycaemic control in ESRD patients who are on haemodialysis. In this study, the GA levels were elevated significantly in ESRD patients with no significant correlation with blood glucose levels,
thus indicating true glucose intolerance \(^{10}\). The mechanism of the elevated GA 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 \(^{11}\). The elevated GA levels may reflect a true impairment of glycaemic control, as reported in uraemic patients. There is a possibility that ESRD patients have glucose intolerance and have high post-prandial hyperglycaemia, which might have resulted in increased GA levels \(^{12}\). Our finding of an increased GA levels and mortality in individuals with macroalbuminuria as well as in individuals with an impaired renal function is in agreement with literature: Several studies reported a high cardiovascular morbidity and mortality among individuals with albuminuria \(^{13,14,15}\) and among individuals with impaired renal function \(^{16}\).

The finding that macroalbuminuria is predictive of accelerated renal function loss also is compatible with data from other studies. Iseki et al \(^{17}\) showed in a large cohort of Japanese individuals who were followed for 17 yr that proteinuria as measured by dipstick was predictive of later risk to reach ESRD.

It also is in line with data in patients with known primary renal disease, in whom proteinuria has been found to be a strong risk marker for progressive loss of renal function \(^{18}\). Surprisingly, however, eGFR did not fall in the group with impaired renal function at baseline. This finding is in line with a recent study in England in individuals with a median eGFR of 28.5 ml/min per 1.73 m\(^2\). The majority of these individuals had stable renal function \(^{19}\). Individuals with impaired renal function at baseline experienced less renal function decline during follow-up compared with the overall population. Although these individuals used more interfering medication, BP, glucose, and cholesterol levels at baseline and during follow-up still were higher (or equal) to values in the total population.

This suggests that the low rate of renal function loss in this group is not due to better medical management of this group. Consequently, we conclude from our data that screening on the basis of determination of renal function impairment and subsequent treatment may be useful to prevent cardiovascular events. It is unlikely, however, that such screening may be helpful to prevent progressive renal function deterioration. Furthermore, a positive correlation between HbA1c levels and GA and Freidwald’s ratio has suggested that there is a trend towards a significance between HbA1c levels and the poor glycemic control, thus indicating the probability of CHD \(^{20}\). Our results therefore suggest that HbA1c and GA may be an important target for intracellular glycoxidation and peroxidation reactions that result in the formation of advanced glycation end products (AGEs) which are further implicated in the causation and the progression of atherosclerosis. Also, chronically deranged glycaemic control in these patients has been associated with increased circulating levels of oxidised LDLc, a highly atherogenic form of LDLc \(^{21}\).

Present study has shown positive correlation of macroalbuminuria with duration of diabetes mellitus with altered GA levels which is in accordance with many previous reports. There is a direct relation between the duration of dialysis and with the development of macroalbuminuria, because of prolonged exposure to hyperglycemia as well as deposition of advanced glycated end products.

**Conclusion**

GA levels measured by the albumin specific protease, ketoamine oxidase method can provide quick and reliable information for evaluating glycaemic control in non-diabetic ESRD patients who received haemodialysis. A new set of recommendations must be considered, regarding
the normal range of the GA levels while assessing the glycaemic control in diabetic ESRD patients. In summary, in non-diabetic patients with ESRD, GA as a marker of impaired glucose metabolism, is a significant predictor of CKD mortality. The results for this study may have important implications: (a) The current definitions for normal glycaemic status may not be appropriate for this population. (b) The high prevalence of dysglycaemia along with high GA levels in nondiabetic ESRD patients on haemodialysis may explain the high risk for cardiovascular disease (CVD). (c) GA may have a role in risk stratification and in the early identification of patients who have non-diabetic ESRD and are at a high risk for CVD.

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References


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