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ORIGINAL ARTICLE

Glycosylated Haemoglobin In Non- Diabetic End-Stage Renal Disease Patients Undergoing Haemodialysis

SANGEETA K*, LAL A K**, GULSHAN M***

ABSTRACT

Background: Glycosylated haemoglobin is widely used as a measure for glycaemic control in patients with diabetes mellitus. The significance of the increased levels of glycosylated haemoglobin in non-diabetic patients with end-stage renal disease, receiving maintenance haemodialysis remains unclear at the present time. It is known that the attainment of glycaemic control is important in these patients. **Objectives:** In this study, an attempt has been made to study glycosylated haemoglobin levels, which may serve as a reliable indicator of integrated glycaemia in these patients. **Material and Methods:** We enrolled 65 non-diabetic end-stage renal disease patients who received haemodialysis and 30 non-diabetic patients without end-stage renal disease for this study. Glycosylated haemoglobin was analysed by a turbidimetric immunoassay by using a Synchron CX system in order to avoid assay interference from uraemia and anaemia in end-stage renal disease patients. **Results:** We found that the average glycosylated haemoglobin levels in non-diabetic end-stage renal disease patients on haemodialysis was 5.23% \pm 1.16 and that in the control group was 4.56% \pm 0.52 ($p < 0.001$). There was no significant difference in the random blood glucose levels between the two groups. Our data indicated that glycosylated haemoglobin levels are elevated in non-diabetic end-stage renal disease patients undergoing haemodialysis. **Conclusions:** We conclude that the elevation in glycosylated haemoglobin level cannot be solely explained by glucose reabsorption from the dialysates and that it reflects true glucose intolerance, which is consistent with increased cardiovascular risk in such patients. Moreover, correlations between glycosylated haemoglobin and the duration of dialysis and the lipid profile of the patient were made, thus indicating the cumulative effect of these factors in regulating the glycaemic status of such patients. Cardiac risk ratio (TC / HDLc) and Freidwald's ratio (LDLc / HDLc), the indicators of coronary heart disease (CHD), were also computed. It was found that these ratios varied significantly with the increase in HbA1c levels in ESRD patients.

Key words: Glycosylated haemoglobin, haemodialysis, glycaemic control.

*Assistant Professor, Department of Biochemistry, Teerthanker Mahaveer Medical College and Research Centre Moradabad, ** Professor & Head of Department of Biochemistry, HIMS, Dehradun, ***Associate Professor Department of Nephrology, HIMS Dehradun.

Corresponding Author:

Dr Sangeeta Kapoor (M.D.Biochemistry)

Assistant Professor
Department of Biochemistry
Teerthanker Mahaveer Medical College and
Research Centre
Moradabad (U.P.) INDIA
Phone No. 09411874572
E-mail address - drsangeeta2000@yahoo.com

Introduction

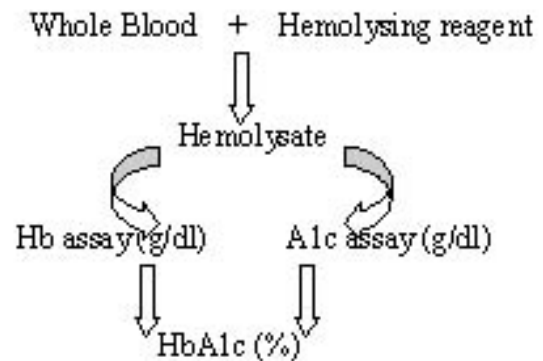
The levels of HbA1c (glycosylated haemoglobin) reflect the glycaemic control during the erythrocyte life span [1]. We have drawn attention to the elevated levels of HbA1c in non-diabetic patients who were on intermittent haemodialysis and found significantly higher HbA1c levels but no correlation with blood glucose. The knowledge of HbA1c 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 [2]. A multitude of causes leading to increased HbA1c levels have been thought of by various scientists viz; glucose in the dialysates, insulin resistance, glucose intolerance, etc [3]. While the precise mechanisms which cause the elevation of the HbA1c levels remain obscure, this test can be a useful adjunct in the detection of carbohydrate metabolism abnormalities and the consequent cardiovascular risk in these patients [4].

Material And Methods

65 patients from the dialysis unit of HIMS were selected as the test group. All of these had received haemodialysis 3 times a week, for at least 1 year. The study also included 30 normal healthy adults, who served as the controls. The exclusion criteria which were considered were acute cases, diabetes mellitus, pregnancy, active infection, HIV seropositivity and treatment with cholesterol lowering drugs, immunosuppressive agents and corticosteroids. Considering the reliability of the immunoinhibition turbidimetric assay of HbA1c due to non-interference by carbamylated haemoglobin and anaemia, it was used.

The Synchron CX system utilizes two unique cartridges, haemoglobin and A1c to determine the HbA1c concentration as a percentage of total haemoglobin. The specific antibodies were combined with HbA1c from the sample to form soluble Ag-Ab complexes. Polyhapten from the reagent then bound with the excess antibodies and the resulting agglutinated complex was measured turbidimetrically[5].

Hb A1c methodology



HbA1c is presented as A1c/Hb ×100. The data are expressed as mean ± S.D. Student’s t-test was employed for statistical analysis and a p value less than 0.05 was considered to be significant and p values less than or equal to 0.001 were considered to be highly significant.

The present study was conducted as per the principles which were laid down by the ethical committee and consent was obtained for performing tests on the patient’s serum samples.

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 HbA1c level was 4.56 %± 0.52. In ESRD patients, the HbA1c level was 5.23%±1.16. Thus, there was a significant elevation of HbA1c levels in non-diabetic ESRD patients who received haemodialysis (p<0.001).

[Table/Fig 1]: HbA1c levels in ESRD patients and control group.

	ESRD patients (n=65)	Controls (n=30)	p.value
Glucose (mg/dl)	109.09± 22.27	106.60± 14.46	0.51
HbA1c (%)	5.23± 1.16	4.56 ± 0.52	0.0002

Fig 1(a): Comparison of Mean Serum Glucose in total between controls and ESRD patients

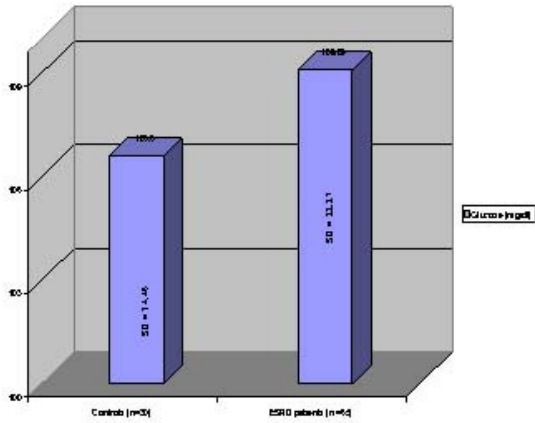
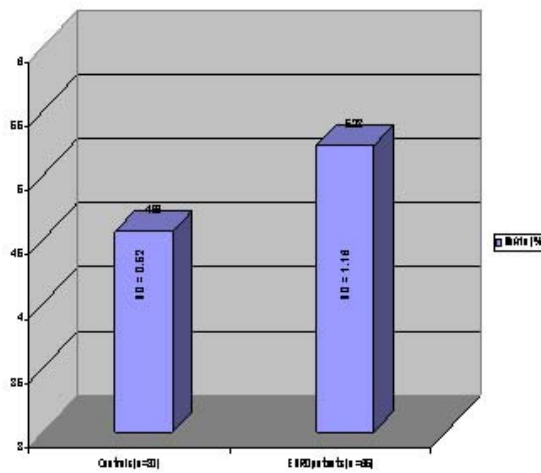


Fig 1(b): Comparison of Mean HbA1c (%) in total between controls and ESRD patients



Also, a significant rise in HbA1c levels was found with the duration of dialysis.

[Table/Fig 2] :HbA1c levels in ESRD patients according to the duration of dialysis.

Duration of dialysis	No. of patients	Mean HbA1c (%)	SD	p.value
< 2 years	39	4.78	0.97	< 0.001
= 2 years	26	5.92	1.10	

A significant rise in the levels of HbA1c was also seen with the rise in the levels of serum triglycerides (TG), serum total cholesterol (TC) and serum LDL cholesterol (LDLc).

[Table/Fig 3]: Correlation of HbA1c levels with TG levels in ESRD patients.

TG (mg/dl)	No. of patients	Mean HbA1c (%)	SD	p.value
= 160	33	4.82	0.84	0.004
> 160	32	5.65	1.30	

[Table/Fig 4]: Correlation of HbA1c levels with TC levels in ESRD patients.

TC(mg/dl)	No. of patients	Mean HbA1c (%)	SD	p.value
= 200	56	5.06	1.02	0.03
> 200	9	6.28	1.43	

[Table/Fig 5]: Correlation of HbA1c levels with LDLc levels in ESRD patients.

LDLc (mg/dl)	No. of patients	Mean HbA1c (%)	SD	p.value
= 150	56	5.06	1.03	0.03
> 150	09	6.30	1.43	

Comparable values of HbA1c were obtained even with decreased values of serum HDLc.

[Table/Fig 6]: Correlation of HbA1c levels with HDLc levels in ESRD patients.

HDLc (mg/dl)	No. of patients	Mean HbA1c (%)	SD	p.value
= 40	43	5.23	1.10	0.97
> 40	22	5.24	1.30	

Significantly elevated values of Cardiac risk ratio (TC / HDLc) and Freidwald's ratio (LDLc /HDLc) were seen in non-diabetic ESRD patients.

[Table/Fig 7]: Cardiac Risk Ratio (TC/HDLc) in ESRD patients and control group.

	ESRD patients (n=65)	Controls (n=30)	p.value
Cardiac risk ratio (TC/HDLc)	5.17 ± 1.50	3.82 ± 0.67	< 0.05

[Table/Fig 8]: Freidwald's Ratio (LDLc /HDLc) in ESRD patients and control group.

	ESRD patients (n=65)	Controls (n=30)	p.value
Freidwald's ratio (LDLc/HDLc)	3.08 ± 1.2	2.37 ± 1.06	< 0.05

A significant correlation of HbA1c levels was seen with Cardiac risk ratio and Freidwald's ratio.

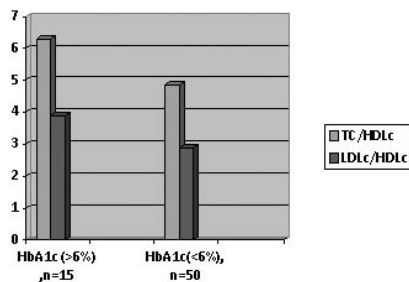
[Table/Fig 9]: Correlation of HbA1c levels with mean Cardiac risk ratio (TC/ HDLc) in ESRD patients.

HbA1c (%)	No. of patients	Mean Cardiac risk ratio (TC/ HDLc)	SD	p.value
>6	15	6.28	0.97	< 0.05
=6	50	4.85	1.50	

[Table/Fig 10]: Correlation of HbA1c levels with mean Freidwald's ratio (LDLc/HDLc) in ESRD patients.

HbA1c (%)	No. of patients	Mean Freidwald's ratio (LDLc/ HDLc)	S D	p-value
≥6	15	3.89	0.54	< 0.05
<6	50	2.90	1.26	

Fig 2 : Correlation of HbA1c level with mean TC/HDLc and LDLc/HDLc ratios in ESRD patients .



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. In this study, the HbA1c levels were elevated significantly in ESRD patients with no significant correlation with blood glucose levels, thus indicating true glucose intolerance [6].

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 [7]. The elevated HbA1c 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 HbA1c levels [8].

Dyslipidaemias are commonly associated with impaired glycaemic control. In this study also, a significant correlation was found between serum HbA1c and TC, TG and LDLc respectively, thus indicating that dyslipidaemia was a concomitant metabolic abnormality with impaired glycaemic control, which was consistent with high cardiovascular risk,

leading to premature cardiovascular disease in the ESRD patients[9].

The statistically non-significant correlation of the mean HbA1c levels with HDLc levels is consistent with the observations made by Menon V, Greene T and Pereira AA et al, where the HDLc levels of the patients remained the same, despite the elevation in the HbA1c levels [2].

Framingham's study had suggested that as the TC/HDLc (Cardiac risk ratio) increases, so does the risk of coronary heart disease (CHD). In populations with low CHD incidences, the average values of the Cardiac risk ratio are below 3.99. LDLc /HDLc (Freidwald's ratio) (0 -3.55) is considered to be an even more accurate measurement of recent cardiovascular disease. In this study, it has been found that both these ratios were significantly ($p < 0.05$) elevated in non-diabetic ESRD patients, as compared to the control subjects. Both the parameters may thus be used for analyzing the probable risk of atherosclerosis in non-diabetic ESRD patients [10].

Furthermore, a positive correlation between HbA1c levels and Cardiac risk ratio and Freidwald's ratio has suggested that there is a trend towards a significance between HbA1c levels and the risk of atherosclerosis, thus indicating the probability of CHD [11].

Our results therefore suggest that HbA1c 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 [2].

Conclusions

HbA1c levels measured by the turbidimetric immunoassay 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 HbA1c

levels while assessing the glycaemic control in diabetic ESRD patients.

In summary, in non-diabetic patients with ESRD, HbA1c as a marker of impaired glucose metabolism, is a significant predictor of CVD mortality (12).

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 HbA1c levels in non-diabetic ESRD patients on haemodialysis may explain the high risk for cardiovascular disease (CVD).
- (c) HbA1c 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 [13].

Limitations

1. A follow up study could not be formulated to study the synergistic contribution of elevated HbA1c levels and dyslipidaemia in CVD mortality in ESRD patients.
2. The precise mechanisms behind the HbA1c level elevation in ESRD patients remain obscure.
3. Direct evidence for the usefulness of this test in the evaluation of hyperlipidaemia could not be provided.
4. The correlation of HbA1c levels with blood glucose measurements at specified time points i.e . fasting and post-prandial blood glucose levels needs to be further contemplated.

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