Haemoglobin A1c level in non-diabetic patients with end- stage renal disease on haemodialysis

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Abstract

Background: Haemoglobin A1c(HbA1c) is widely used to monitor the glycaemic control in diabetic patients. Recently, it has been found useful for the diagnosis of diabetes mellitus. High HbA1c is said to be associated with high risk of coronary vessel disease irrespective of diabetes.

Objectives: to measure HbA1c concentration in patients with end-stage renal disease on haemodialysis and to correlate its concentration with the duration of disease and total cholesterol level.

Methods: sixty non-diabetic patients with end-stage renal disease on haemodialysis were included in the study. They were matched for sex and gender with sixty apparently normal controls.

Results: there was a significant increase in HbA1c concentration in the study group when compared with the controls with a mean HbA1c concentration of 5.67% +0.2 (P-value= 0.000). There was a significant positive correlation between the HbA1c level and the duration of the haemodialysis (p-value<0.05). A strong correlation was found between Hb A1c and the total cholesterol concentration (p-value< 0.05).

Conclusion: Hb A1c is higher in patients with end-stage renal disease when compared with normal controls. The increase in HbA1c correlates with the duration of the haemodialysis and the cholesterol level.

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Introduction:

HbA1c is a haemoglobin compound produced when glucose reacts with the amino group of haemoglobin. The rate of formation is directly proportional to the plasma glucose concentrations[(1)]. It is widely used to monitor the glycaemic control in diabetic patients. A level <7% indicates optimum control[(3)].

Recently, HbA1c has been found to be useful for the diagnosis of diabetes mellitus. A level of > 6.5% is recommended for the diagnosis of diabetes mellitus[(4)].

Another factor that determines HA1c concentration is the red cells life span. Patients with haemoglobinopathies tend to have a lower concentration of HbA1c[(1)].

Some studies have implicated HbA1c level as an independent risk factor for cardiovascular events and the development of atherosclerosis, independent of diabetes status.[(5,6)]

A study by Khaw et al. demonstrated that a raised HbA1c level predicted mortality and cardiovascular disease in patients without diabetes in the community. Persons with HbA1c concentration < 5% had the lowest rate of coronary vascular disease (CVD) and mortality.

End-stage renal disease is a major health problem, with serious implications on the health system and increased morbidity and mortality. Worldwide, it has a prevalence of 1.1 million[8]. In Sudan the incidence is 70-140/million inhabitants/yr[(10)].

Reduced kidney function is recognized as a powerful and independent risk factor for CVD, even after

adjusting for age and diabetic status[11].

Some studies have shown that HbA1c can predict future CVD events among non-diabetic patients in the general population, and it may play a role in risk stratification and early identification of patients with non-diabetic CKD and at risk of developing CVD[12]. The risk for CVD and overall mortality increased continuously with the HbA1c concentration[13].

Some studies found that the average HbA1c level in non-diabetic end-stage renal disease (ESRD) patients receiving haemodialysis was higher than in healthy individuals[14, 15].

It was found that patients with ESRD have higher levels of cholesterol, which correlates with the duration of haemodialysis[16], and it is well-known that hypercholesterolemia is closely linked to CVD[17].

The aim of this study was to estimate the level of HbA1c in non-diabetic patients with end- stage renal disease on haemodialysis and correlate it with the duration of ESRD and total cholesterol concentration.

Materials and Methods:

A cross-sectional, hospital-based study was carried out in Ibn Sina Renal Dialysis Centre and the Academic Charity Hospital. Sixty non-diabetic chronic renal failure patients on haemodialysis were enrolled in the study, together with 60 apparently healthy matching controls. The study was approved by the Research Committee in the University of Medical Sciences and Technology and a written informed consent was taken from all participants. Results of the HbA1c and cholesterol concentration were shown to all participants.

Patients with: diabetes mellitus, anaemia, and on steroids were excluded from the study.

A questionnaire was used to collect the data. Study variables included: age; gender; and duration of renal failure; history of diabetes and drug history. Haemoglobin, mean corpuscular cell volume (MCV) and mean corpuscular haemoglobin (MCHC) were collected from the patients' records.

Venous blood samples for HbA1c were collected in ethylene diamine tetraacetic acid (EDTA) containers. Samples were stored in 2-4 C until time of analysis which was not more than 4 days after collection. Whole blood was used for the analysis. HbA1c was measured by affinity chromatography which is the preferred method in the clinical laboratory. In this method, the glycoselated haemoglobin attaches to the boronate group of the resin and is selectively eluted from the resin bed using a buffer. This method is not temperature- dependant and is not affected by other types of haemoglobin.

Plasma total cholesterol was measured by the cholesterol oxidase method. Venous blood was collected in heparin containers and plasma was separated by centrifugation. Samples were stored at 2-4C until time of analysis.

Data was entered into SPSS version 13 for analysis. A frequency table was constructed regarding the study variables. The HbA1c and total cholesterol of the study groups were presented in mean and standard deviation. Pearson correlation and student t-test were used for testing the significance of the results.

Results:

The study population consisted of 45 males and 15 males. The age distribution showed that 31.7% were in the age group of 20-40; 53.3% were 41-60 years; and 25% were more than 60 years old.

The mean HbA1c concentration in the non-diabetic patients with end-stage renal failure was 5.7% which is significantly higher than that of the controls 5% (p value 0.000) Table 1.

Table 1. Mean HbA1c concentration

Subjects	Mean concentration	SD	P value
Cases	5.7%	0.2	0.000
Controls	5%	0.4	

Regarding the cholesterol concentration, it was significantly higher in the study group (111.6 mg/dl) than in the controls (96.7mg/dl) with a P value of 0.004 as shown in Table 2.

Table 2. Mean serum cholesterol concentration

Subjects	Mean concentration	P value
Cases	111.6 mg/dl	0.004
Controls	96.7 mg/dl	

As shown in table 3 , significant correlation between the HbA1c concentration and the cholesterol concentrations was found (P value 0.007). There was a significant correlation between the HbA1c concentration and the duration of the haemodialysis (P value 0.041); however, serum cholesterol did not show a similar correlation

Table 3. Correlation between the duration of ESRD and HbA1c and cholesterol concentrations

Duration of ESRD	Pearson correlation	P-value
HbA1c conc.	0.265	0.041
Cholesterol conc.	0.095	0.470

Discussion

In this study it was found that the HbA1c level was significantly higher in the ESRD patients than in the controls. This finding was consistent with similar previous studies. One study found that the average HbA1c level in non-diabetic end-stage renal disease (ESRD) patients receiving haemodialysis was 5.99% and in the control group was 5.45% ($p<0.05$).14 Another study found that in non-diabetic control patients, the HbA1c level was 4.56 %+ 0.52 and in ESRD patients, the HbA1c level was 5.23%+1.16 ($p <0.001$)x[15]. Thus, there was a significant elevation of HbA1c levels in non-diabetic ESRD patients who received haemodialysis.

These findings suggest that patients with ESRD have a level of dysglycaemia that may not meet the criteria for a diagnosis of diabetes mellitus. This could be due to the repetitive exposure to high glucose concentrations in the dialysate or a true pre-diabetic state[16]. This higher level of HbA1c predicts a higher risk of mortality and cardiovascular disease in patients with ESRD as was demonstrated by Khaw et al and others[7,12] in addition to their increased risk associated with the renal dysfunction[11].

Interference by carbamylated haemoglobin, which is a chemically modified derivative of haemoglobin due to uraemia, can affect the accuracy of HbA1c measurements, as well as genetic variants of haemoglobin (e.g. HbS trait, HbC trait) and elevated foetal haemoglobin (HbF). These may1 interfere with the analysis causing a falsely higher HbA1c[1].

On the other hand, some factors may affect the interpretation of HbA1c results. Any condition that shortens erythrocyte survival or decreases mean erythrocyte age (e.g., recovery from acute blood loss, haemolytic anaemia) will falsely lower HbA1c test results regardless of the assay method used. The role of renal anaemia, erythropoietin intake, and other factors in chronic renal failure is more difficult to evaluate. Recent reports suggest HbA1c underestimates glycaemic control in diabetic patients on dialysis and that glycated albumin is a more accurate indicator of glycaemic control1.

Hypoglycaemia associated with renal failure is more common than generally thought of. Drugs like: propranolol, salicylates, and disopyramide are among the most commonly implicated agents. Additional triggering events are: alcohol consumption; sepsis; chronic malnutrition; acute caloric deprivation; concomitant liver disease; congestive heart failure; and an associated endocrine deficiency. When no obvious cause can be demonstrated, the hypoglycaemia is referred to as spontaneous. Spontaneous uremic hypoglycaemia has been attributed to deficiency of precursors of gluconeogenesis, that is: alanine- deficient gluconeogenesis: impaired glycogenolysis; diminished renal gluconeogenesis and impaired

renal insulin degradation and clearance; poor nutrition; and, in a few cases, deficiency in an immediate counter-regulatory hormone such as catecholamine and glucagon[18]. All of these factors make HbA1c unsuitable for monitoring of glycaemia in ESRD patients and so search for a more robust indicator is required.

The mean HbA1c concentration in controls is different in this study than the 5.45% mentioned in the literature[14] which emphasizes the need to establish a reference value for Sudanese individuals.

A significant positive correlation was found between the duration of the ESRD and the HbA1c concentration. A similar correlation between cholesterol concentration and HbA1c was also found on top of the significantly higher cholesterol in the study group. Both HbA1c and cholesterol are associated with the development of coronary artery disease and, as patients with ESRD are at an increased risk of developing CVD[7,14], HbA1c can play a role in risk stratification and early identification of non-diabetic patients with ESRD at high risk of developing CVD[12,18]. Moreover, a higher HbA1c level is also associated with an increased relative risk of death from any cause other than CVD[10], underscoring its importance in the follow-up of patients.

No correlation was found between the cholesterol level and the duration of haemodialysis, unlike the published findings which showed a positive correlation[17].This could be due to the relatively small sample size, though it again stresses the need to establish local reference values.

Conclusion

This study has shown that patients with ESRD have a higher HbA1c and cholesterol concentration than controls. A positive and significant correlation between the duration of ESRD and the HbA1c concentration and between HbA1c and cholesterol concentration was noticed.

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