GLYCOSYLATED HAEMOGLOBIN AND DIABETIC CONTROL

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SYNOPSIS

Glycosylated haemoglobin (HbA_1) estimation has been reported to be a useful index in the retrospective assessment of diabetic control. We studied 58 patients with diabetes mellitus who were on treatment. The patients were members of the Diabetic Society of Singapore. They were divided into two groups. The first group, comprising 40 patients, participated in the National Home Blood Glucose Monitoring (NHBGM) programme. The second group, (non-NHBGM), consisting of 18 patients were not included into the programme. Both groups were matched for age, sex and treatment regimens. The indices of metabolic control (glycosylated haemoglobin and blood glucose concentrations) were determined at the commencement and at two monthly intervals over a period of 6 months.

Our results showed that at the commencement of the study, the 58 diabetic patients had a significantly higher glycosylated haemoglobin value (10.6 ± 0.3%; x ± SEM) compared to the normal controls (8.3 ± 0.3%) $p < 0.001$.

The patients on NHBGM showed significant improvements in both the fasting blood glucose concentrations, 134 ± 9mg/dl to 122 ± 8mg/dl ($p < 0.05$), and the grouped blood glucose profile values, 135 ± 8 to 118 ± 5mgm/dl ($p < 0.01$). These improvements in blood glucose control is reflected by the decrease in the glycosylated haemoglobin levels, 10.3 ± 0.4 to 9.3 ± 0.3% (p 0.01). In contrast, no significant changes in these metabolic parameters were observed in the non-NHBGM group over the same study period.

This study shows that glycosylated haemoglobin level is a useful objective marker for monitoring blood glucose control.

INTRODUCTION

A meticulous approach to diabetic control as a measure to delay and prevent the micro-vascular complications of diabetes mellitus has been advocated(1). A setback in the attainment of this aim has been the absence of a reliable index of glycaemia control. The widely used urine and random blood glucose estimations are often misleading and do not provide sufficient information regarding the blood glucose profile throughout the day. Improved methods for monitoring are required. The recent discover of glycosylated haemoglobin (HbA_1), which reflects the integrated blood glucose level of the preceeding four to eight weeks, introduce a potentially valuable tool for the objective assessment of diabetic control.(2, 3)

In 1981, we conducted a study to evaluate the use of glycosylated haemoglobin in the monitoring of diabetic control among patients in Singapore.

METHODS

A total of 58 patients from the Diabetic Society of Singapore participated in the study. They were divided into two groups. The first group, comprising 40 patients, 30 males and 10 females, age 19-76 years ($\bar{x}$ = 50 years) were randomized into the National Home Blood Glucose Monitoring (NHBGM) programme. The second group (non-NHBGM), consisting of 18 patients, 15 males and 3 females, age 20 to 71 years ($\bar{x}$ = 45) did not participate in programme.

Both groups were matched for age and sex and were on comparable treatment regimens for their diabetes. In the NHBGM group, 64% were on oral hypoglycaemic agents, 28% on insulin and 8% were on diet alone. For the non-NHBGM group, the figures were 47%, 35% and 18% respectively. Twenty-six healthy staff members of the hospital comprising 15 males and 11 females, age 22 to 64 years ($\bar{x}$ = 34 years) serves as the normal control subjects.

Blood samples were obtained for the estimations of glycosylated haemoglobin, fasting blood glucose and haemoglobin level from all the diabetic patients and normal controls at the commencement of the study.

Those patients in the NHBGM programme were then taught to measure their blood glucose levels at home using the "Haemo-Glucotest 20-800" test strips or with reflectance meters. They were instructed to perform blood glucose profiles 4 times a day, twice a week for the 6 month study period. Patients in the non-NHBGM group had their fasting blood glucose levels determined in the laboratory at 2 monthly intervals.

Glycosylated haemoglobin were determined for both groups of patients at the end of the 6 month study period. The estimations were done using agar gel electrophoresis method (Corning "Glytrac").

Analyses of results were performed using Student's test and linear regression.

RESULTS

As shown in Table I, at the beginning of the study period, the glycosylated haemoglobin concentration of the 58 diabetic patients was 10.6 ± 0.3% ($\bar{x}$ ± SEM). This was significantly higher when compared to that of the normal subjects of 8.3 ± 0.3% ($p<0.001$). The fasting blood glucose concentration of the patients was 136 ± 6mg% compared with that of normal subjects of 84 ± 4mg% ($p < 0.001$).There was a significant correlation between glycosylated haemoglobin concentration compared with the fasting blood glucose level, $r = 0.76$, $p < 0.001$. The haemoglobin concentration of the diabetic subjects (14.8 ± 0.2 gm/dL) and normal controls (15.0 ± 0.3gm/dL) was comparable. This eliminated anaemia as a factor for their difference in glycosylated haemoglobin value.

TABLE I

Glycosylated Haemoglobin, Fasting Blood Glucose and Haemoglobin Concentrations of 58 Diabetic Patients and 26 Normal Subjects At Commencement of the Study.

	Patients ($\bar{x}$ ± SEM)	Normal Subjects ($\bar{x}$ ± SEM)	P
Glycosylated Hb (%)	10.6 ± 0.3	8.3 ± 0.3	<0.001
Fasting Blood Glucose (mg/dl)	136.7 ± 6.3	84.3 ± 4.3	<0.001
Haemoglobin Concentration (g/dl)	14.8 ± 0.2	15.0 ± 0.3	N.S.

As shown in Table II, the patients on the NHBGM programme demonstrated a significant improvement in the grouped fasting blood glucose concentration 134 ± 9 to 122 ± 8mg/dl ($p<0.05$). Similarly, the decrease in the grouped blood glucose profile values over the 6 month period, 135 ± 8 to 118 ± 5mg/dl, was also statistically significant ($p<0.01$). This improvement in blood glucose level was reflected in the glycosylated haemoglobin levels, a decrease from 10.3 ± 0.4% to 9.3 ± 0.3%, ($p<0.01$), (Table IV).

In contrast, the patients in the non-NHBGM group did not demonstrate significant improvement over the period of study (Table III). The fasting glucose concentrations ranged from 151 ± 19mg/dl to 160 ± 20mg/dl and the glycosylated haemoglobin levels (Table IV) remained unchanged, 10.6 ± 0.7% to 10.4 ± 0.6%.

TABLE II

Glucose Levels of Patients in NHBGM Group

	TIME (MONTHS)			
	0	2	4	6
Fasting Glucose Levels $\bar{x}$ ± S.E.M. (mg/dl)	N.A.*	134 ± 9	129 ± 7	122 ± 8 ($p < 0.05$)
Grouped Glucose Profiles $\bar{x}$ ± S.E.M. (mg/dl)	N.A.*	135 ± 8	131 ± 6	118 ± 5 ($p < 0.01$)

*Not Available

TABLE III

Glucose Levels of Patients In Non-NHBGM Group

	TIME (MONTHS)			
	0	2	4	6
Fasting Glucose Levels $\bar{x}$ ± S.E.M. (mg/dl)	151 ± 19	133 ± 12	142 ± 11	160 ± 20

TABLE IV

Glycosylated Haemoglobin Levels in Diabetic Patients

	TIME (MONTHS)	
	0	6
NHBGM Group $\bar{x}$ ± S.E.M. (%)	10.3 ± 0.4	9.3 ± 0.3 ($p < 0.01$)
Non-NHBGM Group $\bar{x}$ ± S.E.M. (%)	10.6 ± 0.7	10.4 ± 0.6

DISCUSSION

In adults, the major form of haemoglobin in the red cell is haemoglobin A. Glycosylated haemoglobins are minor haemoglobins comprising HbA1c, HBA1a, HbA1b, HbA1d and HbA1e. The term HbA1 (glycosylated haemoglobin) denotes the sum of all these minor haemoglobins, the main fraction being HbA1c. HbA1c was first isolated by

Allen et al(4) and is formed by the addition of a glucose molecule to the N-terminal of the β-chain of haemoglobin A. This reaction is non-enzymatic and the rate of formation depends mainly on the degree of glycaemia that the erythrocytes are exposed to throughout their life span. The process of glycosylation is a post-translational and irreversible event. The level of glycosylated haemoglobin would therefore reflect the average blood glucose level of the preceding four to six weeks. The measurement of glycosylated haemoglobin level would therefore provide a compositive retrospective index for the assessment of glycaemic control(5, 6).

In this study, the raised glycosylated haemoglobin level of the diabetic patients compared to the normal subjects indicates that in a random group of diabetic patients, even though on treatment but without proper methods of monitoring, do not enjoy optimal control.

Our study also showed that an improvement in blood glucose is reflected by a parallel fall in glycosylated haemoglobin(7, 8) level by three to four weeks. Serial measurements of glycosylated haemoglobin will therefore be a useful objective marker for monitoring changes in glucose control. A decline in glycosylated haemoglobin to within the normal range will be obtained as normoglycaemia is established. The improvement in metabolic control in the NHBGM group as compared to the non-NHBGM group further emphasize that self-monitoring of blood glucose is an effective means of achieving optimal control. However, we are aware that increased attention and education given to the group on NHBGM program could have also partly contributed to the improvement.

It is worthy to note that glycosylated haemoglobin reflects the average blood glucose level of the patient retrospectively over the previous four to six weeks but gives no information regarding the flunctuation of blood glucose profiles throughout each day. This limitation fortunately can be overcome with self-measurement of blood glucose. Measurement of glycosylated haemoglobin provides an adjunct to, but should not replace careful blood glucose monitoring.

Glycosylated haemoglobin determination and self-monitoring of blood glucose therefore play important complementary roles for the management of diabetes mellitus. Their availability for clinical use, together with improvement in therapies, would help towards the attainment of a level of metabolic control in the diabetic subjects which was hitherto not possible.

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