Role of HbA1c in management of diabetes mellitus

Aisha A. Al-Ghamdi, *Arab/Saudi Board (IntMed), FACP.*

ABSTRACT

Objective: To represent that glycosylated hemoglobin (HbA1c) is not requested by the physicians in spite of its critical importance in the monitoring of glycemic control and prediction of complications due to diabetes.

Methods: A cross-sectional study was conducted at the outpatient department of King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia, between October 2002 and July 2003. Out of the 265 known patients with diabetes, 130 patients were included in the study, which had HbA1c levels registered in their medical records. Demographic features, smoking habit, presence of hypertension, hyperlipidemia were recorded. Detailed information on diabetes were recorded, which included duration, type (type I or type II) and pattern of treatment, degree of glycemic control (assessed by two-points blood sugar and HbA1c levels). Screening for microvascular complications was recorded.

Results: Only 130 (49%) of the patients with diabetes were included in the study. Poor control was detected in the majority of the patients with diabetes. There was a difference in the detection of poor glycemic control by both methods; HbA1c levels showed poor control in 77% of the patients and by the two-point blood sugar (2-PBS) methods in 69% of the patients. Only 70% of the patients with poor glycemic control by HbA1C showed poor control by 2-PBS ($p=0.7$). Poor control was detected in 45% of the patients using insulin by measuring HbA1c levels, and by measuring 2-PBS in 34% of the patients ($p=0.005$, $p=0.16$). A significant relation was found between HbA1c levels, retinopathy and nephropathy ($p=0.02$, $p=0.05$).

Conclusion: Guidelines of the American Diabetic Association (ADA) regarding proper management of patients with diabetes should be followed to achieve the recommended outcome. Glycosylated hemoglobin levels should be checked every 3 months. Physicians and patients must be advised not to depend solely on 2-PBS results, especially for insulin dependant diabetics.

Diabetes mellitus (DM) is a chronic illness that requires continuous medical care, patient self-management and education to prevent acute complications and to reduce the risk of long-term complications.[1] The incidence of type II DM in children and adolescents has increased dramatically in the last decade and earlier screening should be considered.[2] Although oral glucose tolerance test (OGTT) is a more sensitive and specific test than fasting plasma sugar (FPS) to diagnose DM, it is poorly reproducible and rarely performed in practice. Due to ease of use, acceptability to patients, and lower cost, FPG is the preferred screening and diagnostic test.[1] Acute life-threatening consequences of DM are hyperglycemia with ketoacidosis or the non-ketotic hyperosmolar syndrome. Long-term complications of DM include retinopathy, nephropathy, neuropathy, stroke, ischemic heart disease, and diabetic foot.[3] Monitoring of glycemic status is

considered a cornerstone of care in diabetes. Results of monitoring are used to assess the efficacy of therapy and to guide the adjustment in medical nutrition therapy (MNT), exercise, and medications to achieve the best possible blood glucose control.[4] Americans Diabetes Association (ADA) recommends blood glucose testing by patients through self-monitoring of blood glucose (SMBG) and by health care providers for routine out-patient management of DM.[5] Recently SMBG has revolutionized management of DM as it helps to achieve and maintain specific glycemic goals. Frequency and timing of glucose monitoring should be dictated by the needs and goals of the individual patient, but for most patients with type I diabetes it is recommended 3 or more times daily. The optimal frequency of SMBG for patients with type II diabetes is not known but it should be sufficient to reach glucose goals.[6] Laboratory testing of blood glucose, urine glucose testing, blood and urine ketone testing should be available to providers for use as needed. These tests provide useful information for day-to-day management of DM. Measurement of glycosylated hemoglobin (HbA1c) and glycated serum protein (GSP) can quantify average glycemia over weeks and months, thereby complimenting day-to-day testing.[4,7]

Methods. A cross-sectional study was conducted at the Outpatient Department (OPD) of King Abdul-Aziz University Hospital (KAUH), Jeddah, Western, Kingdom of Saudi Arabia between October 2002 and July 2003. Two hundred and sixty-five known diabetic patients who where regularly followed up at the OPD were selected randomly. One hundred and thirty patients were included in the study as they fulfilled the criteria of the study design, which was measurement of HbA1c, and the remaining patients were excluded.

Data collection. Demographic features were recorded for the patients. Regarding DM detailed information were recorded, which included duration of DM, type of DM (type I or type II), pattern of treatment whether on diet, oral hypoglycemic drugs (OHG), insulin, combined insulin and OHG, degree of glycemic control assessed by 2-point blood sugar and HbA1c levels, poor control if fasting blood sugar >8mmol/l, post prandial blood sugar (PPBS) >11mmol/l and HbA1c >8%, presence of microvascular complications (retinopathy was assessed by history of visual disturbance, history of cataract and fundus examination by an ophthalmologist, nephropathy was assessed by proteinuria or raised serum urea and creatinine after exclusion of other causes, neuropathy; was assessed by a history of numbness or decreased sensation and evidence of decreased sensation or reflexes on neurological examination or evidence of electrophysiological testing). The presence of

hypertension (patient is known hypertensive if the blood pressure is >140/90 mm Hg on more than one occasion), presence of hyperlipidemia (known to have hyperlipidemia or total cholesterol >5.2 mmol/L and triglycerides >2.3 mmol/L) and smoking history (active or passive) were all recorded.

Statistical analysis. Measurement of HbA1c was carried out for 130 patients and only those were considered as the study group, remaining patients were excluded. Data analysis were carried out using Statistical Package for Social Sciences. Mean ± SD was calculated for quantitative data, and frequency for categorical variables. Students' t-Test was used for comparing means of continuous variables. Proportions were compared by Chi-square Test and Fisher's Exact Test if needed. Significance level was set at <0.05 throughout the analysis.

Results. One hundred and thirty (49%) patients who had HbA1c registered and were considered as the study group from the 265 patients. Their ages ranged from 15-80 years and the mean age was 53.5 ± 14.5 years. Male to female ratio was 1:1.4, and the majority was non-Saudi (69%). As shown in (**Table 1**) 41% patients were hypertensive, while 55% of the patients had hyperlipidemia and surprisingly only 7% of the patients were smokers. The mean duration of DM was 10.6 ± 7.6 years and most of the patients were type II (91%). The majority of the patients were on OHG (57%), insulin alone was used by 31% while 8% were on both insulin and OHG and 4% were under dietary control only. Poor control was found by both long-term follow up (HbA1c) in 77%, and short-term follow up (2-point blood sugar) in 69% of the patients. The mean level of HbA1c was 9.7% ± 2 %. **Table 2** illustrates that only 70% of the patients with poor glycemic control by HbA1c showed poor control by two-point blood sugar and 33% of patients with good control by HbA1c showed good control by 2 points blood sugar (p=0.7). Although p value was not statistically significant, but still there was discrimination between the 2 values when comparing the percentage of long-term control and short-term control. Table 3 shows the different values when comparing results of poor glycemic control between patients on insulin with those on OHG alone, it was found that 45% of patients on insulin were poorly controlled by using HbA1c (p=0.005); in contrast to only 34% of the patients which showed poor glycemic control by the two-point blood sugar (p=0.16). For those on OHG (51%) showed poor glycemic control by HbA1c (p=0.01); in contrast to 63% which showed poor glycemic control by the 2-point blood sugar (p=0.02). **Table 4** shows the relation of the microvascular complications to either the long-term follow-up (HbA1c) and the short-term

Table 1 - General characteristics of patients with diabetes.

Variables	n of patients	(%)
Type of diabetes mellitus		
Type I	12	(9.2)
Type II	118	(90.8)
Type of treatment		
Diet	6	(4.6)
OHG	74	(56.9)
Insulin	40	(30.8)
Combined OHG of insulin	10	(7.7)
Long term control (by HbA1c)		
Poor control	100	(77)
Good control	30	(23)
Short term control (2-PBS)		
Poor control	90	(69.2)
Good control	40	(30.8)
Hypertension		
Yes	54	(41.5)
No	76	(58.5)
Hyperlipidemia		
Yes	72	(55.4)
No	58	(44.6)
Smoking		
Yes	10	(7.7)
No	120	(92.3)
Retinopathy		
Yes	64	(49.2)
No	66	(50.8)
Nephropathy		
Yes	40	(30.8)
No	90	(69.2)
Neuropathy		
Yes	74	(56.9)
No	56	(43.1)

OHG -oral hypoglycemic drugs, HbA1c - glycosylated hemoglobin, PBS - points blood sugar

Table 2 - Comparison between degree of control by fasting blood sugar, 2 hours PP and glycosylated hemoglobin levels.

Glycosylated hemoglobin	Short term control Yes n (%)	No n (%)	Total n	(%)
No control	70 (70)	30 (30)	100	(100)
Good control	20 (77)	10 (33)	30	(100)

PP - post prandial

Table 3 - Comparison between short term control and long term control between patients under insulin and oral hypoglycemic drugs.

Blood sugar control	Patients on insulin n (%)	p value	Patients on OHG n (%)	p value
Control by HbA1c		0.005		0.01
No	45 (45)		51 (51)	
Yes	5 (17)		23 (77)	
Control by 2 PBS		0.16		0.02
No	31 (34)		57 (63)	
Yes	19 (48)		17 (43)	

p value is significant if <0.05
HbA1c - glycosylated hemoglobin, PBS - points blood sugar, OHG -oral hypoglycemic drugs

follow up (2-point blood sugar). In patients with poor glycemic control by HbA1c; retinopathy was found in 55%, nephropathy in 35% and neuropathy in 61% of the patients ($p=0.02$, $p=0.05$, $p=0.09$), in contrast to those which showed poor glycemic control by the 2-point blood sugar. Retinopathy was found in 54%, nephropathy in 37% and neuropathy in 62% (p values of 0.09, 0.04, 0.09).

Discussion. This study showed underestimation of HbA1c during routine OPD follow up at KAUH. Only 49% of the total numbers of patients have been considered in the study group. It could be explained by lack of request for the investigation by the physicians, or it could have been requested but was not carried out due to the absence of the reagent or ignorance of the patient by the role it plays in DM management. Glycosylated hemoglobin level represents a glycemic history of the previous 2-3 months (the average erythrocyte life span), and the rate of its formation is directly proportional to the ambient glucose concentration. Standardization of HbA1c measurement is required between laboratories for comparison purposes, which was introduced in 1996 by the National Glycohemoglobin Standardization Program.[4] Ideally HbA1c should be checked every 3 months to determine whether a patient's metabolic control has been achieved and maintained within the target range.[1] This study showed poor glycemic control in 77% of the patients by HbA1c level compared to 69% detected by FPG, 2 hours PPG. This discrimination was noticed by previous researchers.[3] Patients on insulin are better to be followed by HbA1c rather than by FPG and 2 hours PPG. This has been shown by this study ($p=0.005$, 0.16). The high percentages of retinopathy (55%), is significantly correlated with poor glycemic control by HbA1c, which was not detected by high FPG, hours PPG ($p=0.02$, $p=0.09$). Poor control of hypertension and hyperlipidemia will accelerate DM complications.[8,9] This could be attributed to the high percentages of DM complications in this study. Strict glycemic control is important in delaying the onset and slowing the progression of microvascular complications.[10-14] Diabetes Control and Complications Trial[15] and the United Kingdom Prospective Diabetes Study[16,17] have shown that improved glycemic control is associated with decreased rates of retinopathy, nephropathy and neuropathy.[18] In these trials treatment regimens that reduced average HbA1c to 7% were associated with fewer long term microvascular complications.

In conclusion, it was observed that ADA guidelines are not followed, HbA1c level is not optimally used in DM follow up. All methods of detecting glycemic control are applicable, but

Table 4 - Microvascular complications in relation to short term control and long term control.

Type of microvascular complication	Patients with poor glycemic control by HbA1c		p value	Patients with poor glycemic control by 2 PBS		p value
	n	(%)		n	(%)	
Retinopathy	55	(55)	0.02	49	(54)	0.09
Nephropathy	35	(35)	0.05	33	(37)	0.04
Neuropathy	61	(61)	0.09	56	(62)	0.09

p value is significant of <0.05,
HbA1c - glycosylated hemoglobin
OHG - oral hypoglycemic drugs
PBS - points blood sugar

HbA1c is considered the measurement of choice in monitoring the treatment and the complications of DM. It is recommended HbA1c testing be introduced to physicians as well as patients with diabetes as a preventive measure to reduce morbidity and mortality due to complications of diabetes in the community.

References

1. American Diabetes Association. Standards of Medical Care for Patients with Diabetes Mellitus. *Diabetes Care* 2003; 26 (Suppl 1): S33-S50.
2. American Diabetes Association. Type 2 diabetes in children and adolescents (Consensus Statement). *Diabetes Care* 2000; 23: 381-389.
3. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2002; 25 (Suppl 1): S5-S16.
4. American Diabetes Association. Tests of Glycemia in Diabetes. *Diabetes Care* 2002; 25: S97-S99.
5. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM. Tests of glycemia in diabetes (Technical Review). *Diabetes Care* 1995; 18: 896-909.
6. American Diabetes Association. Self-monitoring of blood glucose (Consensus Statement). *Diabetes Care* 1994; 17: 81-86.
7. American Diabetes \Association. Self-monitoring of blood glucose (Consensus Statement). *Diabetes Care* 1987; 10: 93-99.
8. The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary of the third report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486-2497.
9. Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol* 2002; 90: 625-628.
10. The Diabetes Control and Complication Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977-986.
11. The Diabetes Control and Complication Trial Research Group. The relationship of glycaemic exposure (HbA1C) to the risk of development and progression of retinopathy in the Diabetes Control and Complication Trial. *Diabetes* 1995; 44: 968-983.
12. Ohkubo Y, Kishikawa H, Araki E. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; 28: 103-117.
13. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837-853.
14. UK Prospective Diabetes Study Group. Tight blood glucose control and risk of macrovascular and microvascular complications in Type 2 diabetes (UKPDS 38). *BMJ* 1998; 317: 703-713.
15. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977-986.
16. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insuline compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352: 837-853.
17. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352: 854-865.
18. DCCT/EDIC Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000; 342: 381-389.