Research Article

Diabetic Patients Attain their Target Goals in Glycaemic Control at Zagazig University Diabetes Clinic

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Abstract
Background: Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control [2]. However, glycemic control is considered as the main therapeutic goal for prevention of organ damage and other complications of diabetes [4]. HbA1c has been used as the standard measure for long-term glucose control[13], however HbA1c influenced by presence of medical conditions which affect red cell lifespan or glycation of hemoglobin or any condition analytically interfere with its estimation [8]. Glycated albumin formed by non-enzymatic glycation of serum albumin and reflects short-term (2-3 weeks) mean glycemic levels [10]. **Subjects & Methods:** This study was conducted on a total number of 97 subjects which were subdivided as follow: Group I: 21 known diabetic patients without co-morbid condition (renal or hepatic impairment). Group II: 44 known chronic kidney disease & diabetic patients. Group III: 32 known chronic liver disease (with or without renal impairment) & diabetic patients .In addition to the routine investigation, glycated hemoglobin (HbA1c) using Turbidimetric Inhibition Immunoassay (TINIA) technique and glycated albumin (GA) using Enzyme Linked Immunosorbant Assay (ELISA) technique were measured. **Results:** We found that: In diabetic patients without associated co morbid condition, mean (HbA1c) level was 9.25 ± 2.75, 38.1% of patients were controlled (HbA1c < 7 %) while 61.9% were uncontrolled (HbA1c > 7 %). In diabetic & CKD patients, mean (HbA1c) level was 7.88 ±2.52, 45.5% were controlled (HbA1c < 7 %) while 54.5% were uncontrolled (HbA1c > 7 %). There was no statistically significant difference regarding GA while comparing its values between group II and group I. However, there was a significant decrease in HbA1c in group II when compared to group I. There was a significant decrease in HbA1c in group III when compared to group I. On the contrast, there was a significant increase in GA in group III patients when compared to group I. Also it was noticed that there is significant positive correlation between GA and HbA1c, while there is significant negative correlation between GA and albumin. **Conclusion**: It can be concluded that:
- Most of our patients have poor glycemic control. - GA is reliable alternative glycemic marker to HbA1c in CKD patients and in other situations where HbA1c is unreliable.
Key Words: Glycemic control -HbA1c - GA - CKD.

Introduction
Diabetes mellitus (DM) is a metabolic disorder of hyperglycemia due to insulin deficiency, or insulin resistance or both[1]**.** DM is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control[2]**.** DM is characterized by chronic hyperglycemia together with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin secretion, insulin action or both. These are associated with the development of the specific microvascular complications like retinopathy, which can lead to blindness, nephropathy with potential renal failure, and neuropathy. The latter carries the risk of foot ulcers and amputation and also autonomic nerve dysfunction. Diabetes is also associated with an increased risk of macrovascular disease[3]**.** Glycemic control is considered as the main therapeutic goal for prevention of organ damage and other complications of diabetes. Several large clinical trials have demonstrated that tight blood glucose control correlates with reduction of microvascular complications of diabetes. Therefore, achieving glycemic control is a

critical metabolic goal because hyperglycemia contributes to the progression of diabetes mellitus by affecting both ß-cell function and insulin sensitivity[4]**.** The Fasting plasma glucose is an excellent test for "in the moment" glucose levels, but it does not provide detailed information about the time course trend of the glucose levels. The HbA1c test, however, is a marker of the average glucose levels spread over a two- to three - month period[5]**.** HbA1c provides a reliable measure of chronic glycemia and correlates well with the risk of long-term diabetes complications, so that it is currently considered the test of choice for monitoring chronic management of diabetes. Among diabetics, the blood glucose levels increase in the blood and the glucose attaches to the hemoglobin molecule in a concentration-dependent manner, so HbA1c levels are directly proportional to the blood glucose levels[6]**.** Lowering HbA1c to approximately 7% or less has been shown to reduce microvascular complications of diabetes, and, if implemented soon after the diagnosis of diabetes, it is associated with long-term reduction in macrovascular disease. Therefore, a reasonable HbA1c goal for many non pregnant adults is < 7%. Lowering HbA1c to < 7.0% can be achieved with mean plasma glucose of (150-160 mg/dl); ideally, fasting and pre-meal glucose should be maintained at < 130 mg/dl and the postprandial glucose at < 180 mg/dl[7]**.** However, HbA1c influenced by presence of medical conditions which affect red cell lifespan or glycation of hemoglobin or any condition analytically interfere with its estimation[8]**.** So, there has been increasing interest in nontraditional glycemic markers as alternatives to HbA1c because of the situations that can be reduced the validity of HbA1c test[9]**.** Glycated albumin (GA), a ketoamine formed by non-enzymatic glycation of serum albumin, reflects short-term (2-3 weeks) mean glycemic levels[10]**.**

Accordingly, the measurement of GA seems useful not only as an alternative index of glycemic control in conditions in which HbA1c is unreliable, but also for identifying impaired control of blood glucose before any noticeable changes in HbA1c may occur.[11]**.** Also, we can calculate the GA to HbA1c ratio (GA/HbA1c) by dividing GA by HbA1c because GA/HbA1c can sensitively represent glucose variability[12]**.**

Subjects & Methods

Comparative Cross sectional study was performed in Diabetes Clinic, Internal Medicine Department , Faculty of Medicine, Zagazig University Hospitals.

Subjects*:*

The study included ninety seven patients which were divided into 3 groups:

Group I: 21 known diabetic patients without co-morbid condition (renal or hepatic impairment), 11(52.4%) males and 10(47.6%) females ,their ages range from 15-80 years with a mean value of 46.95±19.54 years, 6(28.6%) type 1 DM and 15(71.4%) type 2 DM .

Group II: 44 known chronic kidney disease & diabetic patients, 15(34.1%) males and 29(65.9%) females, their ages range from 25-95 years with a mean value of 64.68±10.63 years, 1(2.3%) type 1 DM and 43(97.7) type 2 DM.

These patients were divided into 4 subgroups according to estimated GFR:

Subgroup 1 (CKD stage 2); with estimated GFR 60-89 ml/min/1.73m², including 12 patient.
Subgroup 2 (CKD stage 3); with estimated GFR 30-59 ml/min/1.73m², including 14 patient.
Subgroup 3 (CKD stage 4); with estimated GFR 15-29 ml/min/1.73m², including 10 patient.
Subgroup 4 (CKD stage 5); with estimated GFR < 15 ml/min/1.73m², including 8 patient.

Group III: 32 known chronic liver disease (with or without renal impairment) & diabetic patients, 13 (40.6%) males and 19 (59.4%) females, their ages range from 46-75 years with a mean value of 62, 03±7.74 years, all were type 2 DM.

These patients were divided into 2 subgroups according to renal impairment:

Subgroup 1; without renal impairment (estimated GFR ≥ 90 ml/min/1.73m²), including 16 patient.

Subgroup 2; with renal impairment (estimated GFR ≤ 90 ml/min/1.73m²), including 16 patient.

Inclusion criteria:

Subjects included in this study are patients with age more than 14 years old, of both sex, diagnosed with diabetes mellitus either type 1 or 2, based on the diagnostic criteria of American Diabetes Association , 2010, with or without other co morbid conditions (renal or hepatic impairment) , who attend to Zagazig University Diabetes Clinic

Exclusion criteria:

Patients suffered from these criteria were excluded from participation in this study:

(1) Not known diabetic patients.
(2) Patients with age ≤ 14 years old.
(3) Patients with recent blood loss.
(4) Blood transfusion within last three months.
(5) Known Glucose-6- phosphate dehydrogenase deficiency patients, sickle-cell disease patients and thalassemia patient.
(6) Thyroid dysfunction.
(7) Patients taking medications as vitamin c, high dose aspirin, ribavirin, etc..

Laboratory investigations:

Routine investigations in the form of:
Fasting blood glucose – 2 hour postprandial plasma glucose - Complete blood count - Kidney function tests - Liver function tests- Lipid profile - Estimated GFR using Cockcroft - Gault Equation.
Special investigations in the form of:
* Glycated Hemoglobin (HbA1c) using Tina-quant® HbA1c Gen.2 Turbidimetric inhibition immunoassay (TINIA)
* Serum Glycated albumin: using Human Glycated Albumin (GA) ELISA Kit.

Statistical analysis

All data were analyzed using SPSS 20.0 for windows, MedCalc Statistical Software version 15.8. Continuous variables were expressed as the mean±SD, median and range while the categorical variables were expressed as a number (percentage). Continuous variables were checked for normality by using Kolmogorov-Smirnov test. One-Way ANOVA was used to compare normally distributed variables in three or more groups. Kruskal-Wallis H (KW) test was used to compare non-normally distributed variables in three or more groups. Post-hoc Fisher's Least Significant Difference test (LSD) tests were used according to homogeneity of variances.
For independent sample of two groups; normally-distributed data were analyzed using Independent Student t (t) test.

Pearson product-moment correlation coefficient was used to assess correlation between HbA1c, GA, GA/ HbA1c and various study parameters if data is parametric while Spearman's rank correlation coefficient (Spearman's rho) was calculated if data is not parametric.
$p < 0.05$ was considered statistically significant (S), $p < 0.005$ was considered highly statistically significant (HS), and $p \geq 0.05$ was considered non statistically significant (NS).

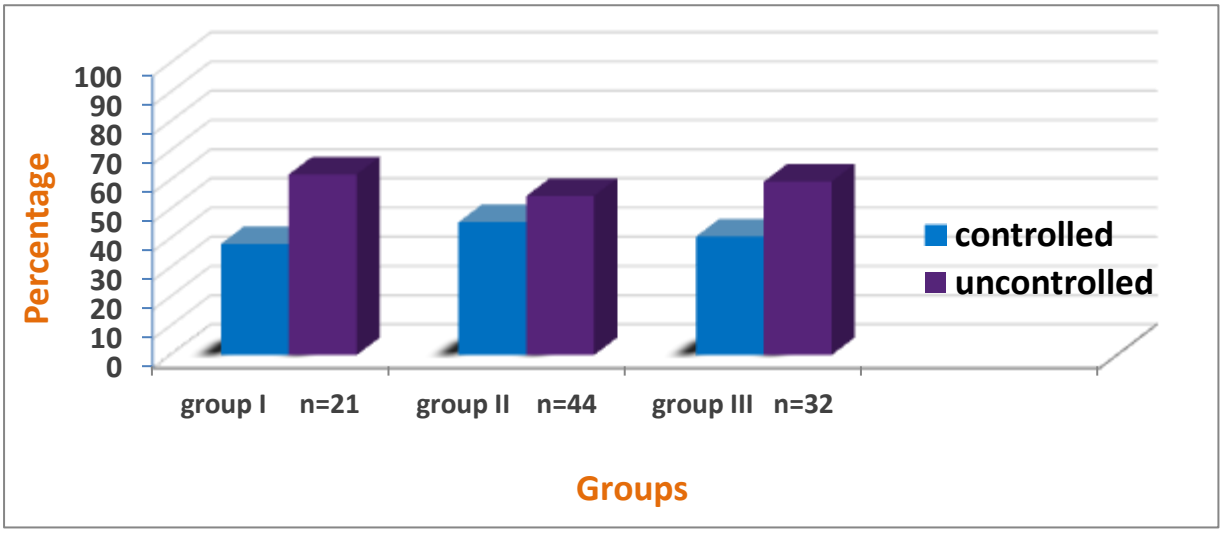
Results

- By using HbA1c as a glycemic control parameter (HbA1c <7%), percentage of controlled patients was 38.1% in group I, 45.5% in group II, and 40.6%in group III. On contrary to that, by using the three parameters of glycemic control together (FBG < 130 mg/dl**,** 2hPP < 180 mg/dl**,** HbA1c < 7%), percentage of controlled patients was 9.5% in group I, 22.7% in group II, and 9.4% in group III.
- Statistically, there was no significant difference regarding FBG between studied groups. However, there was a significant increase in 2hPP in group I when compared to group II, while there was no significant difference between group I and group III & between group II and group III.
- There was significant difference in HbA1c % between studied groups. Mean HbA1c % was 9.25 ± 2.75 in group I, 7.88 ± 2.52 in group II, and 7.38 ± 1.83 in group III. There was a significant increase in HbA1c % in group I when compared to group II and group III, while there was no significant difference between group II and group III.
- There was significant difference in GA% between studied groups. Mean GA% was 12.32 ± 8.65 in group I, 11.74 ± 8.87 in group II, and 17.16 ± 11.13 in group III. There was a significant increase in GA% in group III when compared to group II, while there was no significant difference between group I and group II & between group I and group III.
- There was significant difference in GA/ HbA1c between studied groups. Mean GA/ HbA1c was 1.36 ± 0.95 in group I, 1.55 ± 1.19 in group II, and 2.37 ± 1.52 in group III. There was a significant increase in GA/ HbA1c ratio in group III when compared to group I and group II, while there was no significant difference between group I and group II.
- No significant differences were found in FBG, 2hPP, HbA1c%, GA%, GA/ HbA1c ratio among population with renal impairment (Group II subgroups (n=44)) and diabetic patients with normal renal function (Group I (n=21))
- There were no significant differences in FBG, 2h PP, HbA1c%, GA%, GA/HbA1c ratio between chronic liver disease with or without associated renal impairment (n=32).

Table (1): Comparison of glycemic control parameters of the studied population (n=97):

	Group I Diabetic (n=21)		*Group II* Diabetic with renal impairment (n=44)		*Group III* Diabetic with liver impairment (n=32)		Test	P
	No	%	No	%	No	%		
FBG (mg/dl)							**F**	0.666 (NS)
Mean± SD	158.67 ± 57.01		168.5 ± 81.08		173.16 ± 66.51			
Median (Range)	178 (93 – 291)		150.5 (67 – 400)		170.5 (82 – 378)		0.408	
2hPP (mg/dl)							**KW**	**0.038 (S)**
Mean± SD	333.38 ± 104.6		266.26 ± 111.87		280.5 ± 88.8			
Median (Range)	349 (154 – 509)		251 (115 – 544)		275.5 (125 – 460)		6.56	
HbA1c (%)							**F***	**0.021 (S)**
Mean± SD	9.25 ± 2.75		7.88 ± 2.52		7.38 ± 1.83			
Median (Range)	9.5 (5.3 – 14.6)		7.2 (4.9 – 15.6)		7.29 (4.4 – 11.7)		4.04	
GA (%)							**F***	**0.046 (S)**
Mean± SD	12.32 ± 8.65		11.74 ± 8.87		17.16 ± 11.13			
Median (Range)	9.42 (2.7 – 30.9)		10.28 (2.2 – 35)		14.87 (2.5 – 37.7)		3.19	
GA/ HbA1c							**KW**	**0.028 (S)**
Mean± SD	1.36 ± 0.95		1.55 ± 1.19		2.37 ± 1.52			
Median (Range)	1.27 (0.27 – 3.47)		1.11 (0.3 – 4.1)		2.50 (0.33 – 5.35)		7.14	

Figure (1) Percentage of controlled patients by HbA1c in each group



Discussion

HbA1c has been used as the standard measure for long-term glucose control[13]. American Diabetes Association recommend that HbA1c <7% is a reasonable goal for many non-pregnant adults. Lowering HbA1c to <7% can be achieved with mean plasma glucose of (150-160 mg/dl); ideally, fasting and pre-meal glucose should be maintained at < 130 mg/dl and the postprandial glucose at <180 mg/dl [6]. HbA1c is influenced by RBC survival, because the average lifespan of RBC is 120 days, HbA1c reflects mean glucose levels over the preceding two to three months. Falsely elevated HbA1c in relation to a mean blood glucose concentration can be achieved when RBC turnover is decreased, resulting in a dispro-

portionate number of older RBC. Inversely, increased RBC turnover leads to a greater proportion of younger RBC and falsely lowed HbA1c values[14]**.** Several factors in CKD patients have a significant impact on HbA1c values that may be falsely low or high. These factors including: the lifespan of the RBCs, uremic environment, blood transfusions and (rHuEpo)[15]**.** Despite these considerations, current international guidelines for diabetes care in CKD recommend that "target HbA1c for people with diabetes should be <7.0%, irrespective of the presence or absence of CKD" [16]**.** Among patients with CLD, anemia, portal hypertension, hypersplenism, and variceal bleeding can be common complications. These factors can contribute to longer or shorter red RBC survival and can lead to alteration of the HbA1c. Factors such as nutritional anemia can lead to increased RBC survival and falsely elevated HbA1c levels, whereas bleeding and hemolysis can lower RBC survival time and falsely lower HbA1c values[17]**.**

The aim of our study is to assess how many diabetic patients attain their target goals of glycemic control by assessment of: Fasting blood glucose, 2hpp, HbA1c in those with or without other co morbidities (CKD or CLD), and assess GA and GA/HbA1c ratio as alternative markers of glycemic control.

In our study, in diabetic patients without associated co morbid condition (n=21), mean (HbA1c) level was 9.25 ± 2.75., 38.1% of patients were controlled (HbA1c <7%) while 61.9% were uncontrolled (HbA1c >7%). However, by using the three parameters of glycemic control together (FBG < 130 mg/dl**,** 2hPP <180 mg/dl**,** HbA1c <7%), percentage of controlled patients was only 9.5% while 90.5% were uncontrolled. Using the three glycemic control parameters together is more reliable than using HbA1c alone for assessment of glycemic control as the major drawback of HbA1c as a single metric is that it gives no information about glycemic variability[18]., but most studies depend on HbA1c alone in assessment of glycemic control. Using GA as alternative glycemic control index is reliable, however measurement of GA by different assays lack standardization, values vary widely among methods[19], and no cutoff values are present to define controlled and uncontrolled diabetic patient. Also, due to these limitations, GA/HbA1c ratio need to be more investigated. In diabetic & CKD patients (n=44), mean (HbA1c) level was 7.88±2.52, 45.5% were controlled (HbA1c <7%) while 54.5% were uncontrolled (HbA1c >7%). By using the three parameters of glycemic control together (FBG <130 mg/dl, 2hPP < 180 mg/dl, HbA1c <7%), only 22.7% of patients were controlled while 77.3% were uncontrolled. the large percent of uncontrolled CKD patients explain why the number of ESRD patients increase among diabetics. There was a significant decrease in HbA1c% in diabetic & CKD patients when compared to diabetic patients without associated co morbid condition, this significant decrease in HbA1c% in diabetic & CKD patients that associated with the significant decrease in 2hPP.Another factor could contribute to the significant decrease in HbA1c% in diabetic & CKD patients, when compared to diabetic patients without associated co morbid condition, which is the increased rate of hemoglobin turnover in CKD patients that leads to decreased exposure time to ambient glucose that in turn lowers the extent of non-enzymatic binding of glucose to hemoglobin that lead to a lower value of HbA1c[20]**.**

There was a significant decrease in HbA1c% in diabetic & CLD patients when compared to diabetic patients without associated co morbid condition. Lower HbA1c is due to the increased erythrocyte catabolism.

There was a significant increase in GA% in diabetic & CLD patients when compared to diabetic patients without associated co morbid condition, despite absence of significant difference between them in FBG& 2hpp, this due to decrease of albumin catabolism. There was a significant increase in GA/ HbA1c ratio in diabetic &CLD patients when compared to diabetic patients without associated co morbid condition, this significant increase is independent of the plasma glucose level.

Conclusion

* Most of our patients could not reach their target goals of glycemic control.
* HbA1c, GA and GA/ HbA1c ratio are not accurate parameters in assessment of glycemic control among CLD patients.

* HbA1c and GA are valid glycemic control markers in CKD patients; however GA is a more accurate in pre-dialysis patients

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