Serum Glycated Albumin and GA/HbA1c Ratio as a New Markers of Glycemic Control in Children with Type 1 Diabetes Mellitus

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ABSTRACT

Introduction: Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia and accompanied by long term damage, dysfunction and failure of various organs. Several studies have shown that Glycated Albumin (GA) is more reliable DM monitor and a better marker of glycemic control in patients with fluctuating and poorly controlled type 2 DM. Moreover, serum GA is not affected by factors that affect hemoglobin metabolism.

The aim of the study: To study the value of serum glycated albumin as a new marker for glycemic control in diabetic children.

Methods: 30 diabetic children were included in the study in addition to 20, sex and age matched apparently healthy children as a control group. The associations among HbA1c, GA, and GA/HbA1c ratio were examined, referred and managed in Children's Hospital, Minia University.

The results: Plasma glucose, GA and HbA1c measurements were done at baseline, after the 1st and after the 3rd months for all the subjects. GA levels strongly correlated with HbA1c% in the diabetic group. The mean GA and HbA1c values were significantly lower in control group than in diabetic group ($p<0.001$). GA, HbA1c and the ratio decreased significantly within 4 weeks, but GA showed a significantly larger decrease than HbA1c.

Conclusion: GA seems to be more accurately reflect short term glycemic control than HbA1c.

Keywords: Glycated albumin (GA); Hemoglobin A1C (HbA1c); Type 2 Diabetes Mellitus (T2DM)

INTRODUCTION

Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels [1].

The use of diagnostic markers has shown that early diagnosis and treatment have the potential to prevent diabetic complications [2].

HbA1c is widely used for evaluation of long-term glycemic control and it provides an index of average blood glucose level during the past 2-3 months [3].

However, the use of HbA1c has some limitations as it may not be suitable for short term glycemic control and also in conditions that affect Hb metabolism as anemia [4].

THE AIM OF THE WORK

The aim of this work was to study the value of serum Glycated Albumin (GA) as a new marker for glycemic control in diabetic children.

PATIENTS AND METHODS

This case-control study had been carried out in the NICU of El-Minia University Hospital. Thirty diabetic children were recruited from the pediatric outpatient DM clinic and had already been diagnosed as diabetic patients for more than 6

months duration according to the standard ADA criteria [5], during the period from September 2017 to June 2019. Their ages ranged from 2-14 years old (12 males and 18 females). In addition to 20 age and sex matched children (8 males and 12 females) were included as a control group. Patients excluded those who were anemic, and those with liver dysfunction, malignancy, thyroid diseases, diabetic complications, and patients on steroids.

All patients and controls were subjected to full history taking, including name, age, sex, residence, age of onset and duration of diabetes; and thorough clinical examination, including anthropometric measurements: (weight, height and body mass index) for each child and measures were plotted on the Egyptian Growth Charts (2002); where body weight obtained in kilogram and taken with the child in light clothes with no shoes. Height obtained in centimeters using Stadiometer. BMI was calculated according to the known formula; BMI=Weight (kg)/Height (m2); followed by complete systemic examination. Laboratory investigations, including the followings: Hb Level, Fasting blood sugar, postprandial blood sugar, fasting serum Glycated Albumin (GA), HbA1c serum level, and GA /HbA1c Ratio.

Investigations were done at the start of the study for both diabetic and control groups and during the follow-up visits after one month and after three months for the diabetic group.

Five ml of whole venous blood was withdrawn by a sterile vein puncture and divided into 3 tubes: one ml of venous blood was collected in EDTA containing tubes (Ethylene-diamine-tetra-acetic acid) for glycated hemoglobin level; 2 ml on a plain plastic tube were allowed to clot in the incubator at 37°C and after coagulation samples were centrifuged at 3000 rpm for 10 minutes to obtain serum. Serum is then used for measuring glycated albumin level; and 2 ml on a plain plastic tube were allowed to clot in the incubator at 37°C and after coagulation samples were centrifuged at 3000 rpm for 10 minutes to obtain serum that is then used for measuring two hours post prandial blood sugar.

Statistical methods

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 20.

Descriptive statistics were done for parametric quantitative data by mean, standard deviation and minimum & maximum of the range, while they were done for categorical data by number and percentage.

Analyses were done for parametric quantitative data between the two groups using independent sample t test, and for non-parametric quantitative data using Mann Whitney test, while they were done for qualitative data using Chi square test.

Analyses were done for parametric quantitative data within the same group at different time's using paired sample t test.

Correlation between two quantitative variables was done by using Pearson's correlation coefficient. Correlation coefficient ranges from (0-1):- weak (r=0-0.24), fair (r=0.25-0.49), moderate

(r=0.5-0.74), strong (r=0.75-1). The level of significance was taken as (p value<0.05)

The study was carried out according to the principles of declarations of Helsinki, and its appendices [6] and was approved the hospital ethical review board in El Minia university hospital (code 75a, March, 2015). Written informed consents from patients' caregivers were obtained for the use of their study-related information and for participation in the ongoing research.

RESULTS

Table 1 show that there is no significant difference between diabetic and control groups as regard demographic and anthropometric data, while there is a significant difference between both groups in percentile of both height and weight; and not in BMI percentile.

Table 1: Demographic and anthropometric data of diabetic and control group.

	Diabetic group	Control group	p value
	(N=30)	(N=20)	
Age (years)			
Range	(3-15)	(3-13)	0.58
Mean ± SD	9.33 ± 3.51	8.8 ± 2.98	
Sex (no %)			
Male	12 (40%)	12 (60%)	0.166
Female	18 (60%)	8 (40%)	
Wt (kg)			
Range	(15-61)	(15-50)	0.792
Mean ± SD	36.43 ± 12.02	37.3 ± 10.15	
Wt Percentile			
Range	(24-98)	(45-98)	0.012[b]
Mean ± SD	70.1 ± 18.88	83.8 ± 17.24	
Ht (cm)			
Range	(90-160)	(92-158)	0.614
Mean ± SD	131.83 ± 20.81	134.75 ± 18.41	
Ht Percentile			
Range	(2-93)	(30-97)	0.001[b]
Mean ± SD	38.1 ± 25.92	63.6 ± 21.51	
BMI (kg/m²)			

Range	(16.6-24.1)	(17.5-24)	0.813
Mean ± SD	20.19 ± 2.13	20.34 ± 1.97	
BMI[a] Percentile			
Normal	14 (46.7%)	6 (30%)	
Overweight	8 (26.7%)	7 (35%)	0.499
Obese	8 (26.7%)	7 (35%)	
BMI[a] Percentile			
Range	(45-99)	(39-98)	0.471
Mean ± SD	82.23 ± 14.88	85.5 ± 16.55	

[a]Body mass index; [b]p value<0.05 is significant.

Table 2 shows that there is significant difference between diabetic and control groups as regards glycated albumin, glycated hemoglobin, fasting blood sugar, 2 hours postprandial and glycated albumin/glycated hemoglobin, but there is no significant difference between hemoglobin or albumin level between both groups.

Table 2: Laboratory data of diabetic and control group.

	Diseased group (N=30)	Control group (N=20)	p value
Hb (g/dl)			
Range	(9.9-14.3)	(11-14.6)	
Mean ± SD	12.21 ± 1.13	12.31 ± 0.91	0.76
Albumin (g/dl)[a]			
Range	(3.6-5.5)	(3.8-5.5)	
Mean ± SD	4.54 ± 0.41	4.52 ± 0.51	0.87
HbA1c (%)			
Range	(4.1-9.6)	(4.5-6.4)	
Mean ± SD	7.21 ± 1.36	5.62 ± 0.52	<0.001[b]
GAa (%)			
Range	(10.75-27.75)	(6.6-14.2)	
Mean ± SD	19.15 ± 4.04	11.08 ± 2.11	<0.001[b]
GA/HbA1c Ratio[c]			
Range	(1.89-3.8)	(1.46-2.21)	
Mean ± SD	2.7 ± 0.44	1.94 ± 0.2	<0.001[b]
FBS (mg/dl)[d]			
Range	(60-309)	(70-125)	
Mean ± SD	140.1 ± 62.38	97.7 ± 15.69	0.001[b]
2 hrs PP (mg/dl)[e]			
Range	(150-420)	(118-182)	
Mean ± SD	272.63 ± 147.2	156.5 ± 16.41	<0.001[b]

[a]Glycated Albumin; [b]p value<0.05 is significant; [c]Glycated Albumin / Glycated Hemoglobin; [d]Fasting Blood Sugar; [e]2 Hours Postprandial.

Table 3 shows that there is a significant difference between serum levels of glycated hemoglobin at baseline and after three months, between after one month and after three months, and between baseline and after one month.

Table 3: Comparison of laboratory data of diabetic group.

	At baseline	After 1 month	After 3 months	P1	P2	P3
HbA1c (%)						
Range	(4.1-9.6)	(5-9.2)	(4.9-9.8)			
Mean ± SD	7.21 ± 1.36	7.13 ± 1.18	6.67 ± 1.15	0.483	0.046[b]	0.036[b]
GA (%)[a]						
Range	(10.7-27.7)	(7.7-23.25)	(5.1-25.5)			
Mean ± SD	19.15 ± 4.04	15.91 ± 3.75	14.83 ± 4.48	<0.001[b]	<0.001[b]	0.021[b]
GA/HbA1c[c] ratio						
Range	(1.89-3.8)	(1.45-3.16)	(0.83-5.59)			

Mean ± SD	2.7 ± 0.44	2.23 ± 0.47	2.36 ± 0.82	<0.001[b]	0.013[b]	0.299
FBS (mg/dl)[d]						
Range	(60-309)	(70-267)	(79-180)			
Mean ± SD	140.1± 62.3	151.1± 46.46	119 ± 28.19	0.266	0.054	0.002[b]
2 hrs PP (mg/dl)[e]						
Range	(150-420)	(165-380)	(144-331)			
Mean ± SD	272.6 ±147	273 ± 62.1	216 ± 48.46	0.985	0.064	<0.001[b]

[a]Glycated Albumin; [b]p value<0.05 is significant; [c]Glycated Albumin/Glycated Hemoglobin; [d]Fasting Blood Sugar; [e]2 Hours Postprandial.

There was a significant difference between glycated albumin measurement at base line and after one month, between base line and after three months and between the after one month and after three months.

Also, there is a significant difference between GA/HbA1c ratios between baseline and after one month, baseline and after three months.

There is a significant difference between FBS & 2 hrs postprandial BS after one month and after three months.

Table 4 showed that there is a significant positive correlation between HbA1c measurements at baseline, after one month and after three months and the BMI of diabetic group.

Table 4: Correlation between HbA1c & GA and clinical data of diabetic group.

	HbA1c		GA[a]		HbA1c[b]		GA		HbA1c		GA	
	Baseline		Baseline		After 1 month		After 1 month		After 3 month		After 3 month	
	R	p value	R	p value	R	p value	R	p value	R	p value	R	p value
Hb	0.058	0.762	0.024	0.9	0.012	0.952	0.02[c]	0.89	0.215	0.253	0.07	0.685
Albumin	0.081	0.669	0.152	0.423	0.023	0.905	-0.084	0.658	0.089	0.638	-0.06	0.732
Age	-0.185	0.328	0.054	0.779	-0.207	0.273	0.026	0.89	0.158	0.404	0.113	0.552
Wt (kg)	0.037	0.845	0.264	0.158	0.025	0.894	0.143	0.45	0.338	0.067	0.269	0.15
Ht (cm)	-0.22	0.243	0.049	0.797	-0.255	0.174	0.022	0.906	0.18	0.34	0.13	0.492
BMI[d]	0.632	<0.001	0.536	0.002[c]	0.595	0.001[c]	0.21	0.266	0.47	0.009[c]	0.37	0.044[c]
DM (yrs)[e]	-0.055	0.773	0.137	0.47	-0.103	0.588	0.053	0.78	-0.035	0.856	0.146	0.44

[a]Glycated Albumin; [b]Glycated Hemoglobin; [c]p value<0.05 is significant; [d]Body Mass Index; [e]duration of Diabetis Mellitus in years.

There is a significant positive correlation between GA measurements at baseline and after three months and the BMI of diabetic group; while that at one month is not positively correlated.

There is no significant correlation between GA and age, weight, height, duration of diabetes, Hb or albumin levels.

Table 5 shows that there is significant positive correlation between HbA1c measurements at baseline and that after one month and after three months.

Table 5: Correlation between HbA1c and studied laboratory data of diabetic group at baseline and during follow up visits.

	HbA1c[a]					
	Baseline		After 1 month		After 3 months	
	R	p value	R	p value	R	p value
HbA1c						
Baseline			0.893	<0.001[d]	0.377	0.040[d]
After 1 month	0.893	<0.001[d]			0.525	0.003[d]
After 3 months	0.377	0.040[d]	0.525	0.003[d]		
GA b						
Baseline	0.605	<0.001[d]	0.646	<0.001[d]	0.592	0.001[d]
After 1 month	0.372	0.043[d]	0.47	0.009[d]	0.552	0.002[d]
After 3 months	0.32	0.084	0.445	0.014[d]	0.704	<0.001[d]
GA/ HbA1c Ratio[c]						
Baseline	-0.293	0.116	-0.225	0.232	0.172	0.363
After 1 month	-0.248	0.187	-0.258	0.169	0.222	0.237
After 3 months	-0.02	0.917	0.036	0.85	0.269	0.151

[a]Glycated Hemoglobin; [b]Glycated Albumin; [c]Glycated Albumin/ Glycated Hemoglobin Ratio; [d]p value<0.05 is significant.

There is significant positive correlation between HbA1c measurements at baseline, after one month and after three months and GA measurements at baseline and after one month. But, there is no correlation between HbA1c at baseline and GA measurement after 3 months.

But there is no any significant correlation between HbA1c measurements and GA/HbA1c ratio at three measurements.

Table 6 shows that there is a significant positive correlation between HbA1c measurements at baseline and between GA measurements at baseline and after one month.

Table 6: Correlation between GA and studied laboratory data of diabetic group.

	Glycated Albumin					
	Baseline		After 1 month		After 3 months	
	R	p value	R	p value	R	p value
HbA1c[a]						
Baseline	0.605	<0.001[d]	0.372	0.043[d]	0.32	0.084
After 1 month	0.646	<0.001[d]	0.47	0.009[d]	0.445	0.014[d]
After 3 months	0.592	0.001[d]	0.552	0.002[d]	0.704	<0.001[d]
GA[b]						
Baseline			0.798	<0.001	0.736	<0.001*
After 1 month	0.798	< 0.001			0.844	<0.001*
After 3 months	0.736	< 0.001	0.844	<0.001		
GA/HbA1c Ratio[c]						
Baseline	0.492	0.006 [d]	0.506	0.004	0.436	0.016 [d]
After 1 month	0.335	0.07	0.639	<0.001	0.579	0.001
After 3 months	0.401	0.028[d]	0.556	0.001	0.691	<0.001[d]

[a]Glycated Hemoglobin; [b]Glycated Albumin; [c]Glycated Albumin/ Glycated Hemoglobin Ratio; [d]p value<0.05 is significant.

There is significant correlation between GA measurements at baseline and GA measurements after one month and three months.

Also, there is a significant positive correlation between GA measurements at baseline and after one month and between base line HbA1c/GA ratios.

There is a significant positive correlation between GA measurements after one month and after three months and after one-month HbA1c/GA ratio.

There is a significant positive correlation between GA measurements at baseline, after one month and after three months and after three months HbA1c/GA ratio.

But there is no any correlation between HbA1c measurements at baseline and GA measurement after three months.

No correlation between GA measurement after three months and base line HbA1c/GA ratio.

Also, there is no correlation between baseline GA measurement and after one-month HbA1c/GA ratio.

DISCUSSION

The combination of severe insulin deficiency and physical and psychosocial changes makes the management of children T1DM difficult [7].

Many studies have left areas of uncertainty about HbA1c; the most widely used marker of glycemic control over the preceding 2 to 3 months; Glucose levels during the 30 days before the test have the biggest impact on HbA1c, variability of RBCs lifespan affects the HbA1c levels and also the turnover of HbA1c is very slow because of the long half-life of hemoglobin [8].

Also, it is possible that diabetic individuals with disease duration<3 months would be missed if tested by HbA1c (Lower sensitivity and accuracy) [9].

HbA1c can be influenced by various clinical factors such as anemia (by increasing the proportion of young erythrocytes in the blood and reduced red-blood cell lifespan), recent transfusion, iron deficiency, metabolic acidosis or frequent erythropoietin injection [10].

Compared to HbA1c, GA responds much sooner to changes in glycemic levels, reflecting short-term glycemic control over the previous 2 to 3 weeks [11].

In our study, there was a significant difference in weight and height percentile but not in anthropometric data between diabetic and control group. This was in agreement with Satyavani, et al., [12]. Also, Furusyo et al., agreed with us as regards that both of GA and HbA1c was not influenced by sex and they found that GA measurements can be used to screen for diabetes regardless of age and sex [13].

In the first follow up visit for the patients in our study, both GA and GA/HbA1c ratio decreased significantly, while HbA1c not significantly decreased.

Takahashi et al., & Inaba et al., reported that both GA and HbA1c and the ratio decreased significantly at 16 weeks than at baseline and GA showed a significantly larger percent decrease than HbA1c. The rapid decrease in GA reflects the faster turnover of plasma albumin than that of RBC [10,14].

Koga et al., agreed with us about the positive correlation between HbA1C and BMI [15], and Yoshiuchi et al., agreed with us about the positive correlation between GA and BMI, in childhood T1DM in Japan [16]. While Wang et al. found an inverse relationship between BMI and GA [17].

Takahashi et al. and Selvin et al. agreed with us about the strong relationship between BS readings both FBS and PPS, and both HbA1C & GA [10,18].

Also, our study agreed with Woo et al., about no correlation of GA and serum albumin level [19] and with Miyashita et al., who studied GA levels in obese T2DM .

Koga et al. reported that serum GA levels could be affected by various conditions with abnormal metabolism of albumin. Under certain conditions with shortened albumin metabolism, such as hyperthyroidism, nephrotic syndrome or administered glucocorticoid treatments, serum GA levels are apparently low, whereas it may be high when albumin metabolism is prolonged, as in liver cirrhosis [15].

In our study there was a positive correlation between GA levels and GA/HbA1c ratio and HbA1c levels. This is in agreement with Takahashi et al. study in type 2 diabetic patients [10].

CONCLUSION

This prospective study suggests that GA & GA/HbA1c Ratio are a useful markers for assessing short term glycemic changes in children with type1 diabetes mellitus. They are useful in the assessment of the early improvement of T1DM under treatment.

RECOMMENDATIONS

- Use of GA for short term glycemic control in diabetic children to avoid complication of hypoglycemic and hyper glycemic complications in children.
- GA should be used in glycemic control in diabetic children with anemia, haemodialysis and haemoglobinopathies.

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