ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Glycated Albumin And Glycated Albumin To Hemoglobin A1C Ratio Are Indicators Of The Glycemic Control State In Children With Type-1 Diabetes.

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ABSTRACT

Glycation among various proteins is known to be increased in diabetic patients compared with non-diabetic subjects.The significance of glycated albumin (aGA,GA% and GA% /HbA1C %) compared with fasting Blood glucose (FBG) and glycated hemoglobin (HbA1c) will be evaluated as an indicator of the glycemic control state in children with type-1 diabetes.A total of 100 subjects with type 1 diabetes.In addition, 38 healthy subjects were used as controls. Information including gender, age, duration of disease, insulin dose, height, and weight was obtained. The associations among the daily profile of glucose and FBG, GA, HbA1c, GA: HbA1c ratios were examined within the controlled and uncontrolled subtypes of type 1 diabetes**.** The mean FBG, aGA, GA%, and GA%: HbA1C% ratio, levels were significantly higher in diabetic than non-diabetic controls.GA (%) showed a significantly positive correlation with FBG. However, GA%; HbA1C% ratio showed a significantly negative correlation with FBG and HbA1C%. A significant increase of level of GA% was found in patients with T1DM. It is a promising better measure to estimate blood glucose variability.GA% and the GA%/HbA1C% ratio could advance the field of personalized medicine in management of type 1 diabetes.

Keywords: Type 1 diabetes, glycated albumin, Glycated hemoglobin (HbA1C), GA: HbA1c ratio.

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ISSN: 0975-8585

INTRODUCTION

Type 1diabetes is the result of the auto immune destruction of pancreatic islet β cells due to a failure in immune tolerance[1]. Glycation among various proteins is known to be increased in diabetic patients compared with non-diabetic subjects [2]. Glycated hemoglobin (HbA1C) is commonly used as the gold standard index ofglycemic control in management of diabetes treatment [3].However, it has been accepted for the assessment of long-term glycemic control. The most abundant circulating plasma proteins is Albumin .It is exposed to non-enzymatic glycation by the same proses like the hemoglobin[3].As with glycol hemoglobin, the level of glycated albumin is known to increase in uncontrolled diabetic patients. It has a shorter half-lifeof about 17 days than the 120-day life of thered cell. So it reflects blood glucose concentrations over a shorter retrospective period than does glycohemoglobin[4-6].

Factors that shorten red blood cell (RBC) survival lead toHbA1C lower values inrelation to glycemia [7-8].On the other hand, cases with iron deficiency anemia presents higher HbA1C values relative to plasma glucose levels [9, 10].When cases with iron deficiency anemia are treated with iron supplements, HbA1C transiently decreases because lifespan of erythrocytes shortens [11, 12].

Glycated albumin is influenced with disorders of albumin metabolism not by disorders of hemoglobin metabolism. It shows lower values in relation to glycemia in patients with hyperthyroidism, nephrotic syndrome [13], and administration of glucocorticoidas albumin metabolism increases. Furthermore, Smoking was reported to lower GA in relation to plasma glucose levels. Hypertrigly ceridemia and cases with nonalcoholic fatty liver disease (NAFLD) with high alanine aminotransferase (ALT) levels [14- 17] show lower values in relation to glycaemia. Meanwhile, it shows higher values relative toglycemia in patients with liver cirrhosis[18, 19] and hypothyroidism [13] in which album in metabolism decreases. The rate of albumin glycosylation is about 10 times the rate of hemoglobin [20-22], suggesting that Glycated albumin levels begin to fall before lowering glycol hemoglobin levels after treatment of a hyperglycemic state. Measurement of glycated albumin is reflecting the average blood glucose levels of the past 2-3 weeks while glycol hemoglobin values indicate control over a period of 2-3 months.

Moreover, Saisho et al reported that GA to HbA1c ratio rather than GA itself is a useful index of glucose excursion and related to beta cell function in type 1 diabetes [23].This ratio is affected by short-term blood glucose fluctuations, diabetes and obesity [24].However, knowing that about 50% of A1C is produced during the 30–35 days prior to measurement; both GA and A1C are affected by any significant alteration in plasma glucose during this period. So the GA: A1C ratio mayreflect the fluctuations in glycemic control over the short term [25, 26].

The aim of the present study was to evaluate the clinical usefulness of glycated albumin (aGA, GA% and GA%:HbA1C% ratio)compared with fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) to evaluate glycaemia control in children with type-1 diabetes.

MATERIALS AND METHODS

Subjects

A total of 100 subjects with type 1 diabetes (55 females and45 males, mean age 13.07 ±3.67years, range 4-18 years)attending the Pediatrics endocrine Clinic in Centre of Excellence in National Research Centre .We performed the study, between July 2017 and November 2018.This study is a part from a project no.11010154 done at the National Research Centre, Cairo, Egypt.

The exclusion criteria were: type 1 DM patients with evident organ system disease like hemolytic anemia, patients suffering from other autoimmune diseases, obesity and patients receiving drugs e.g. corticosteroids. Also, cases with diabetic complication that had influence on protein metabolism, e.g. liver dysfunction, thyroid disease and renal failure were excluded. Diabetic children whose duration of disease was less than 6 months were excluded because of the possibility that the GA/A1C ratio would vary greatly owing to rapid improvements in glycemic control. In addition, 38 healthy subjects (24 girls and 14boys, mean age 11.94 ±4.12years, range 4.1-18 years) were used as controls. It is a prospective cross-sectional case control study.

All patients and healthy subjects gave informed consent form to participate in the present study, approved by National Research Centre Ethics Committee.

Information including gender, age, duration of disease, insulin dose, height, and weight was obtained. The weight and height of the participants were measured up to 0.01 kg and 0.1 cm using a Seca Scale Standing Balance and a Holtain Portable Anthropometer (Holtain Ltd, Crymych, Wales, UK). Body mass index (BMI) was calculated for each subject as weight in kilograms divided by height in meters squared. The landmarks, instruments used, and techniques followed were those recommended by the international biological program [27].

Biochemical Analysis

Peripheral venous blood samples after 12 hrs. of fasting were withdrawn from all participants by venipuncture under complete aseptic conditions ; two milliliters EDTA blood for HbA1C estimation and five milliliters of blood were left to clot then sera were separated and aliquited, part of sera are used for determining levels of fasting glucose , AST , ALT and albumin by Erba xl -300 Mannheim Gmbh Germany and rest of sera were uniquely labeled and stored at -20ºc for further determination of the Glycated albumin. Human glycated albumin levels were estimated using Elab science kit Cat No E-EL-H1993 which employs a Sandwich -ELISA principle. HbA1C levels were determined using STANBIO KIT (USA) via Biosystems BTS-302 Photometer (Barcelona) .

Each patient performed self-monitoring (or by parents) of blood glucose at seven points a day. The associations among the daily profile of glucose were used to assess whether glycemic targets are being achieved. Blood glucose and A1C goals for type 1 diabetes across all pediatric age-groups an HbA1C% goal of, 7.5% (58mmol/mol) and fasting blood glucose is 90–130 mg/dL (5.0–7.2 mmol/L) is recommended across all pediatric age-groups [28,29].

Statistical analysis:

The standard computer program Statistical Package for the Social Sciences (SPSS) for Windows, release 17.0 (SPSS Inc.,USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD).

Comparison between groups was made using Student t test for continuous variables and Chi-Square tests for categorical variables. Pearson's and Spearman's correlation tests (r=correlation coefficient) were used for correlating normal and nonparametric variables, respectively. Linear multiple regression was run to predict GA%. For all tests, a P-value of less than 0.05 was considered significant.

RESULTS

The study included 100patients with type 1 diabetes (45males and 55females) and 38 healthy volunteers (14 males and 24 females). All the patients with diabetes were on intensive insulin therapy regimen. Table 1 shows the descriptive data of T1DM cases including: (minimum and maximum reading, mean and SD) of age, BMI, disease duration and insulin dose.

Table 1: The descriptive data of T1DM cases

		Age years	BMI Kg/ M^2	Duration years	Insulin U/KG
N	Valid	100	100	100	100
Mean		13.07	20.89	5.33	1.21
Median		13.0	20.32	5.0	1.12
Std. Deviation		3.67	4.93	3.32	.61
Minimum		4.00	12.45	0.50	.32

ISSN: 0975-8585

		Age years	BMI Kg/ M^2	Duration years	Insulin U/KG
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Median		13.0	20.32	5.0	1.12
Std. Deviation		3.67	4.93	3.32	.61
Minimum		4.00	12.45	0.50	.32
Maximum		18.00	25.58	16.00	2.0

Table2 shows the descriptive data of T1DM cases and controls including: (minimum and maximum reading, mean, median, SD and percentiles) of aGA, GA%, GA%: HbA1C% ratio and FBG. All parameters showed higher levels in all percentiles in cases than controls.

Table 2: The descriptive laboratory data T1DM cases and controls

		Absolute glycated albumin Pmol/ml	GA%	GA%/ HB1AC %	Fasting blood Glucose (mg/dL)	Absolute glycated albumin Pmol/ml	GA%	GA%/ HB1AC%	Fasting Blood glucose (mg/dL)
Items		Controls				T1DM cases			
N		38	38	38	38	100	100	100	100
Mean		486.00	7.96	1.33	81.35	811.84	14.76	1.90	162.36
Median		390.00	8.19	1.53	80.00	632.50	11.99	1.39	160.00
Std. Deviation		308.78	4.04	.59	8.57	690.95	13.69	1.81	36.63
Minimum		40.00	3.00	.54	70.00	25.00	2.90	.31	100.00
Maximum		3075.00	15.89	2.03	100.00	5495.00	85.81	10.73	354.00
Percentiles	5	47.50	3.00	.54	70.00	57.50	3.53	.45	115.95
	25	95.00	4.22	.71	72.50	144.25	4.88	.58	140.00
	50	390.00	8.19	1.53	80.00	632.50	11.99	1.39	160.00
	75	600.00	10.43	2.00	89.00	1249.50	20.56	2.74	180.75
	90	887.00	15.02	2.00	93.00	1436.50	24.65	3.48	201.00
	95	1055.50	15.89	2.03	97.50	1541.75	29.98	4.23	211.50

Table 3 shows comparison between anthropometric and laboratory data of patients and controls. The mean FBG, aGA, GA%, and GA%: HbA1C% ratio, levels were 162.36 ±36.63 mg/dL, 811.84 ±690.9 Pmol/ml,14.76 ±13.69 % and 1.90 ±1.81 , respectively in diabetic group. All were significantly higher (P<.000, .033,.034,.019)respectively. Mean while, there were no significant difference in age and gender among diabetic children and controls (P =.147 and .548).

Table 3: Comparison of demographic and laboratory measures between Cases and Controls

1=CASES 2=CONTROLS		N	Mean	Std. Deviation	Sig. (2-tailed)
Age(yrs.)	1	100	13.07	3.6716	.147
	2	38	11.94	4.1216	
BMI(kg/ m2)	1	100	20.89	4.93	.007*
	2	38	18.19	3.87	
HBA1C%	1	100	8.02	.97	.000*

ISSN: 0975-8585

	2	38	5.6	.73	
Fasting Blood Glucose (mg/dL)	1	100	162.36	36.63	.000*
	2	38	81.35	8.63	
Hb (g/dL)	1	100	12.94	1.02	.041*
	2	38	12.51	.915	
Albumin PMOL/ml	1	100	6012.86	629.79	.016*
	2	38	6358.34	584.64	
Absolute glycated AlbuminPmol/ml	1	100	811.84	690.95	.033*
	2	38	486.87	308.78	
GA%	1	100	14.76	13.69	.034*
	2	38	7.96	4.04	
GA% /HBA1C%	1	100	1.90	1.81	.019*
	2	38	1.33	.75	

* significant

We compared Albumin Pmol/ml, aGAPmol/ml, GA% and GA% / HBA1C% ratio in diabetic patients with controlled diabetes(HbA1C% level<7.5) and uncontrolled patients(HbA1C% level ≥7.5).Tables4 shows Comparison of laboratory measures between the two groups according to HbA1C% level. A significant difference between groups was noted as regards the mean levels of FBG (mg/dL) and HbA1C% (P=.000).While, Albumin Pmol/ml ,aGAPmol/ml, GA% ,GA% / HBA1C% showed no significant differences between means in both groups.

Table 4: Comparison of laboratory measures between the groups according to HbA1C% level

	HbA1C%	N	Mean	Std. Deviation	Sig. (2-tailed)
Age years	>= 7.5	67	13.28	3.45	.241
	< 7.5	33	12.42	4.25 7	
BMI	>= 7.5	67	21.09	4.99	.412
	< 7.5	33	20.28	4.76	
Insulin U/KG	>= 7.5	67	1.215	.618	.402
	< 7.5	33	1.315	.506	
FBG 130(mg/dL)	>= 7.5	67	169.1	36.7	.000*
	< 7.5	33	141.9	27.98	
HBA1C%	>= 7.5	67	8.400	.76	.000*
	< 7.5	33	6.888	.59	
Hb	>= 7.5	67	12.85	.95	.103
	< 7.5	33	13.18	1.18	
Albumin Pmol/ml	>= 7.5	67	6104.	617.77	.283
	< 7.5	33	5972.	529.54	
aGA Pmol/ml	>= 7.5	67	849.2	663.28	.660
	< 7.5	33	938.6	545.45	
GA%	>= 7.5	67	15.63	14.80	.875
	< 7.5	33	16.16	8.47	
GA%;HbA1C%	>= 7.60	67	1.818	1.32	.171

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	HbA1C%	N	Mean	Std. Deviation	Sig. (2-tailed)
Age years	>= 7.5	67	13.28	3.45	.241
	< 7.5	33	12.42	4.25 7	
BMI	>= 7.5	67	21.09	4.99	.412
	< 7.5	33	20.28	4.76	
Insulin U/KG	>= 7.5	67	1.215	.618	.402
	< 7.5	33	1.315	.506	
FBG 130(mg/dL)	>= 7.5	67	169.1	36.7	.000*
	< 7.5	33	141.9	27.98	
HBA1C%	>= 7.5	67	8.400	.76	.000*
	< 7.5	33	6.888	.59	
Hb	>= 7.5	67	12.85	.95	.103
	< 7.5	33	13.18	1.18	
Albumin Pmol/ml	>= 7.5	67	6104.	617.77	.283
	< 7.5	33	5972.	529.54	
aGA Pmol/ml	>= 7.5	67	849.2	663.28	.660
	< 7.5	33	938.6	545.45	
GA%	>= 7.5	67	15.63	14.80	.875
	< 7.5	33	16.16	8.47	
GA%;HbA1C%	>= 7.60	67	1.818	1.32	.171
	< 7.60	33	2.367	1.28	

BMI, body mass index; FBG, fasting blood glucose ;
aGA, Absolute glycated Albumin
* significant

Table 5 shows Comparison of laboratory measures between group1=controlled cases FBG less than or equal 130mg/dL and group 2 = high FBS more than 130(mg/dL). The mean levels of FBG (mg/dL) andHbA1C% were significantly different .As regard ,the mean levels of aGAPmol/ml,GA% and GA% /Hb1AC% no significant differences were found.

Table 5: Comparison between the groups according to FBG level

	1=controlled FBS≤130mg/dL 2= high FBS >130mg/dL	N	Mean	Std. Deviation	Sig. (2-tailed)
Age years	1	22	12.3333	3.92216	.316
	2	78	13.2162	3.64543	
BMI	1	22	21.1576	4.76671	.805
	2	78	20.8678	4.94662	
Insulin U/KG	1	22	1.3420	.41372	.257
	2	78	1.1970	.54019	
FBG (mg/dL)	1	22	120.5455	8.52854	.000*
	2	78	170.8919	34.32951	
HBA1C%	1	22	7.3000	.93452	.000*
	2	76	8.1670	.92087	
Hb (g/dL)	1	22	13.2909	1.22510	.087

ISSN: 0975-8585

	2	76	12.8804	.97683	
Albumin (Pmol/ml)	1	22	6170.6842	641.95301	.404
	2	78	6044.4554	594.78039	
aGA (Pmol/ml)	1	22	684.6923	550.41172	.428
	2	78	893.8444	622.00083	
GA%	1	22	12.0155	8.50489	.338
	2	78	16.2334	14.15135	
GA%;HbA1C%	1	22	1.5917	1.39761	.414
	2	78	2.0137	1.69392	

* significant

Next we assessed the correlation between GA% and age, gender and BMI within children with type 1 diabetes. No significant association was found between GA% and these parameters (r = .088; p = .359,r=.044 .P=.646,r=.058.P=.543) respectively.

Then, the correlations between different indexes were evaluated. Table 6 shows the results of correlation between the each index. GA(%)showed a significantly positive correlation with FBS and aGA (r = .344; p = 0.014)and(r = .986; p = .000) respectively. However, GA%; HbA1C% ratio showed a significantly negative correlation with FBG and HbA1C% (r = -.279; p = 0.039) and(r = -.323; p = 0.020) respectively.

Table 6: The results of correlation between the each index

	GA%/ HbA1C%		FBG(mg/dL).		GA%		aGAPmol/ml		HbA1C%	
	r	p	r	p	r	p	r	P	r	p
GA%;HbA1C%	1.000	.	-.279	.039	-.027	.434	-.059	.357	-.323	.020
FBG (mg/dL).	-.279	.039	1.000	.	.344	.014	.319	.021	.540	.000
GA%	-.027	.434	.344	.014	1.00	.	.986	.000	-.142	.188
aGAPmol/ml	-.059	.357	.319	.021	.986	.000	1.000	.	-.088	.292
Albumin Pmol/ml	-.085	.299	-.098	.271	-.125	.218	-.120	.228	.035	.415
HbA1C%	-.323	.020	.540	.000	.142	.188	.088	.292	1.000	.

A multiple linear regression was run to predict GA% from HbA1C%, Absolute glycated albumin Pmol/ml, Fasting blood glucose, GA% /Hb1AC% These variables statistically significantly predicted GA%, F(5) = 202, p < .000 , R2 = .990. All four variables added statistically significantly to the prediction, p < .000(table7) .

Table7: The multiple regression analysis of glycated albumin (GA %) as the dependent variable

Model 1Dependent Variable, GA%		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	-10.636	.837		-12.702	.000
	Absolute glycated albumin Pmol/ml	.002	.000	.133	4.974	.000
	GA%/ Hb1AC%	6.707	.207	.882	32.447	.000
	Fasting Blood Glucose	-.008	.003	-.031	-2.395	.018
	HbA1C%	1.550	.132	.154	11.749	.000

Dependent Variable, GA%

Predictors: (Constant),Absolute glycated albumin Pmol/ml,GA%/ Hb1AC%, Fasting blood glucose,HbA1C%.

ISSN: 0975-8585

DISCUSSION

Improving glycemic control reduces micro- and macro-vascular complications in patients with type-1diabetes mellitus [30-33]. Knowing that glycated albumin has a short half-life of about 17 days propose the hypothesis it plays an important role in the glycemic control state in children with type-1 diabetes. Also, it may, significantly better estimates glycemic control in diabetic children relative to HbA1C%.

The significantly higher value of FBS, aGA, GA%, HbA1c patients with diabetes compared with the controls suggest that the measurement of this markers play role in the glycemic state in diabetic patients. Our data, in accordance with other studies [1, 21-23].Moreover, Roohk et al. reported that glycated albumin values for diabetic patients are 2- to 5-fold higher than normal levels [23].Our study showeda mean value about 2foldshigher than normal mean level.

The study showed no relation between ages, sex or body mass index in the studied group. Koga etal. reported that there is a negative association of BMI with GA, due to obesity-related inflammation reduces the rate of album in synthesis and increases its catabolic rate [33] but we exclude obese diabetic from the study. Evaluating the mean levels of FBG, aGA and AG% according to glycemic control on the basis of the HbA1c%,no statistical significantly different results were recorded except for FBG. Also, no significant correlation was recorded between HbA1C% and serumaGA and GA% in diabetic patients. This could be explained by the fact that both represent markers at different duration. The HbA1c marker is the long term diagnostic marker of diabetes so demonstrate the glycemic status of diabetic patients in preceding two months. While measurement of GA provides an index of short term glycemic change over a short period of 2weeks in diabetic patients [22].

We compared Albumin Pmol/ml ,aGAPmol, GA% and GA% / HBA1C% ratio in diabetic patients with controlled diabetes (HbA1C% level<7.5) and uncontrolled patients(HbA1C% level ≥7.5) .Results in this study showed that 33 patients had good glycemic control based on the HbA1c assay, compared to 22 ones in FBG evaluation.HbA1C% is not always a sensitive indicator of blood glucose variability. GA (%) showed a significantly positive correlation with FBG. However, GA%; HbA1C% ratio showed a significantly negative correlation with FBG and HbA1C%.

Saisho et al., has been reported that the ratio of GA% to HbA1c% reflected postprandial glucose excursion and relates to β-cell function in both type 1 and type 2 diabetes [34].Matsumoto et al. demonstrated that GA%: HbA1c% ratio is affected by short-term blood glucose fluctuations. SO it could be a better marker for glycemic variability than HbA1c% in type 1 diabetes [35].The present study demonstrated that GA%: HbA1c% ratio was higher in uncontrolled diabetic children.

Finally, a multiple linear regression was run to predict GA% from HbA1C%, Absolute glycated albumin Pmol/ml, Fasting blood Glucose, GA% /Hb1AC% .These variables statistically significantly predicted GA%,

Potential weaknesses in this study, is that we did not evaluate postprandial glucose level. Postprandial hyperglycemia is closely related to the development of diabetic complications [34]. From this view point, it will be included in our new study which will include complicated cases of children with type1 diabetes.

GA is a potential disease marker in the diagnosis of diabetes mellitus. In addition, the most appropriate cut-off point of the glycated albumin assay for the diagnosis of diabetes mellitus is not clear; it has not yet been approved by the Food and Drug Administration[1, 36].The GA/A1C ratio can be determined with simultaneous estimation of GA and A1C and can be generally used in regular clinical practice to evaluate short-term blood glucose fluctuations on individual bases [37-39]. It will be helpful to clinicians for evaluation the response a short time after, the initial treatment of diabetes. It might be useful in monitoring of diabetes associated complications especially in diabetic nephropathy as HbA1c% may not be reliable [40-41].

CONCLUSION

GA% is a significantly higher in children with type 1 diabetes. It is a promising better measure to estimate blood glucose variability. The GA/A1C ratio can be generally used in regular clinical practice to

evaluate short-term blood glucose fluctuations on individual bases. GA% and the GA%/HbA1C% ratio could advance the field of personalized medicine in type 1 diabetes.

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