Glycated albumin and glycated albumin/ glycated haemoglobin ratio decrease with increasing BMI compared to Glycated haemoglobin in Type 2 diabetes patients

Iman El –Sherif[1], Mohamed I. Shoeir[1], Mohamed M. Mohey El Din Awad[1], Amal Fathy[2], Seham Ahmed[1]

[1] Internal Medicine Department, Faculty of Medicine-Suez Canal University, Ismailia, Egypt
[2]Clinical Pathology Department, Faculty of Medicine –Suez Canal, Ismailia, Egypt
Imanelsherif149@yahoo.com

Abstract: Background: Obese T2DM patients are more prone to develop accelerated complications which burdens the global health systems with undue expenditure. Glycated haemoglobin (A1c) had been settled as a gold standard glycemic indicator though it's levels must be prudently interpreted in some patients. Glycatedalbumin (GA) as an alternative, intermediate glycemic indicator is gaining much attention. **Aim:** assessing the correlation of each of glycated albumin and glycated haemoglobin to body mass index (BMI) in T2DM patients **Hypothesis:** negative correlation existsbetween BMI & glycated albumin. **Subjects and methods**: Cross sectional study into which 62 participants- aged 25-60 years - who are T2DM on insulin were recruited at Suez Canal University hospital.None of them was smoker or known to be CLD or DKD patient, none was on regular statins, aspirin or metformin. All had normal CBC and albumin indices, they underwent thorough history taking & examination. anthropometric measurements namely body mass index (BMI) were taken.They were grouped into a non-obese group with BMI <25 Kg/m^2 & obese group whose BMI ≥25 Kg/m^2, each with a sample size of 31 participants. FPG,PPPG, HbA1c, CBC, serum albumin, serum insulin and GA were analyzed.insulin resistance was measured by HOMA-IR. **Results**: GA was insignificantly lower in obese T2DM compared to non-obese (579.3 µmol/L vs 600.0 µmol/L,p- value = 0.631), while GA/HbA1c ratio was significantly low among obese compared to non-obese. (61.1 vs 66.8, p-value= 0.040). Also GA was insignificantly lower in obese with insulin resistance (615.0 ±177.5 µmol/L) than obese with no insulin resistance (550.0±148.2 µmol/L) and also lower than non-obese with insulin resistance (637.4±153.0 µmol/L).Similarly GA/HbA1c ratio was lower in obese with &without insulin resistance (mean 57.6 ±SD 12.8 & mean 64.1 ±SD 9.0 respectively) compared to GA/HbA1c ratio in non-obese with & without insulin resistance (mean 66.9 ±SD 11.0 & mean 66.7 ±SD 9.1 respectively). **Conclusion:** This study showed that care to be paid while interpreting GA levels in obese T2DM as GA and GA/HbA1c ratio are lower in this population.
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1. Introduction

Diabetes has deleterious impact on individual &national productivity. Its socioeconomic consequences have a seriously negative impact on the economies of developed &developing nations **(1).**

In 2014 the global prevalence of diabetes was estimated to be 9% among adults aged 18+ years, where more than 80% of diabetes deaths occurred in low &middle income countries. **(1).**

In 2012, IDF ranked Egypt as the 8th top country with people with diabetes with prevalence 16.62% **(2)** where mean diabetes related expenditure per person in 2012 was only 136.25 USD though the devastating burden of 84.567 deaths related to diabetes among age group 20-79 years & 4.207.30 people with undiagnosed diabetes for same age group. **(3).**

Screening & intervention for diabetes in the earliest stages are advocated for the prevention of diabetic complications &cardiovascular disease. **(4).**

Insulin resistance in diabesity:

T2DM is characterized by increased hepatic glucose output, increased peripheral resistance to insulin action (due to receptor &post receptor defects), &impaired insulin secretion.**(5).**

Insulin resistance and the compensatory hyperinsulinemia, &other components are associated with increased risk of cardiovascular disease; endothelial dysfunction is a prominent feature of insulin resistance syndrome **(6).**

Insulin sensitivity &secretion are reciprocally related; thus, insulin resistance results in increased insulin secretion to maintain normal glucose &lipid homeostasis. The mathematical relation between sensitivity &secretion is curvilinear.**(7).**variant methods for quantification of insulin resistance had been developed ranging from the labor intensive, time consuming, complicated clamp techniques &insulin infusion tests as hyperinsulinemic-euglycemic clamp technique **(8)**down to the less complicated minimalist approaches which were developed as alternatives to

overcome the obstacles of the dynamic clamp techniques as insulin sensitivity test (IST) **(9)**, insulin tolerance test (ITT).**(10)** & oral glucose tolerance test (OGTT).**(11).** Indirect methods as fasting insulin **(9),** Glucose/insulin ratio**(10)** and (Homeostasis model assessment of insulin resistance (HOMA-IR) **(13)** had been advocated for quantification of insulin resistance for epidemiologic & clinical studies as they are simpler & inexpensive quantitative tools.**(8).**

On equal basis, obesity, is the most common cause of insulin resistance, which is associated with a combination of a prevailing post receptor failure to activate tyrosine kinase linked with a decreased number of insulin receptors. While adiposity &insulin resistance are related, they are not necessarily synonymous, &each may make independent & different contributions to increasing the risk of cardiovascular disease. **(14)**

Inflammation & adipocytokines probably play some role in the etiopathogenesis of insulin resistance **(15-17)**. Increased levels of the acute-phase inflammatory marker C-reactive protein (CRP) are related to insulin resistance &the metabolic syndrome, suggesting a role for chronic, low-grade inflammation **(18)** while in a number of prospective studies, CRP increased levels predicted the development of diabetes &cardiovascular disease.**(14, 18,19)**

Glycemic Indicators in use

Diabetes monitoring for protein glycation,is an essential element for the long-term control of the complications of diabetes mellitus.(**20).** Some of these proteins are involved in the development &progression of chronic diabetic complications **(21)**.

Since most hemoglobin resides in the red blood cell, which has a half-life of approximately 120 days, the relative amount of glycated hemoglobin in a patient's blood becomes a living record of glycemia over a period of a few months. The A1c test has become a gold standard for monitoring T2DM, because it has been shown to reliably predict the risk of developing diabetes-related complications. (**22).** lowering HbA1c to 7% has been shown to reduce microvascular complications of diabetes. (**23)**

Most of medical societies had approved HbA1c use for initial diagnosis conditioned that the laboratory uses a standardized approach. **(24)** While other societies approved it for screening for pre-diabetes in non-symptomatic patients. (**23)**

Some confounding medical factors may influence HbA1c levels and so affect its clinical reliability. HbA1c levels decrease due to decreases in red blood cells survival rate as in acute or chronic blood loss & anaemias, it varies according to fluctuations associated with haemoglobin variants as well. **(25)**

Pregnancies decrease HbA1c levels in second trimester to less than 1%, while its levels increase in cases of uremia with normal glucose tolerance, in iron deficiency anaemia where its levels reverse after iron therapy mostly due to increased bone marrow erythropoiesis in response to treatment. (**26)**.

Given the expanding diabetes population, the need for an intermediate glycemic indicator had been recognized. Over the past two decades, many reports have described the measurement of serum protein indicators, as methods to assess glycemic status over intermediate periods (2–4 weeks) that reflect the half-lives of these molecules in serum. Albumin is the largest component of the plasma proteins, representing more than 80% of the total molecules & 60% of the total plasma protein concentration. GA is a ketoamine formed via a non-enzymatic glycation reaction of serum albumin &it reflects mean glycaemia over two to three weeks, both serum &plasma samples can be used.**(4)**

Hence, the concentration of GA in serum, with a half-life of 12–19 days, would be an excellent index of recent ambient glycemia as:

- Albumin can be measured in the blood with fewer issues than Fructosamine.
- It fills the time gap between Self-Monitoring of Blood glucose (SMBG) & A1c.
- It can be measured at approximately 1 month intervals with a turnover time in plasma of 2–3 weeks.
- directly measures the effects of hyperglycemia on the most prevalent plasma protein **(27)**.
- monitors glycemic control in T2DM patients with fluctuating glycemic excursions (**28**).
- It can be used for patients with anemia or hemoglobinopathies for whom the clinically measured hemoglobin A1c level may be inaccurate **(4).**

Among factors that can influence GA values;

1. Increased albumin catabolism induced by chronic micro-inflammatory conditions **(29)**

2. Hyper-metabolic states, as nephrotic syndrome, hyperthyroidism, &glucocorticoid treatment, where GA increases in relation to blood glucose. (**30)**

3. Diminished albumin catabolism, including liver cirrhosis &hypothyroidism decreases GA.(**30)**

GA, HbA1c and GA/HbA1c ratio

Although GA testing was initially viewed as adjunctive to A1c for diabetes management, its utility in detecting short-term changes in glycemic control is supported via evidence;

- Longer duration of T2DM is indirectly associated with GA as the pancreatic β-cell function progressively declines, & insulin resistance ensues, resulting in the failure of insulin secretion from islet

cells, which increases the levels of GA rather than HbA1c levels **(31,32)** as impaired insulin secretion from β-cells can increase blood glucose excursions, which is more sensitively reflected by GA compared to HbA1c. **(33)**

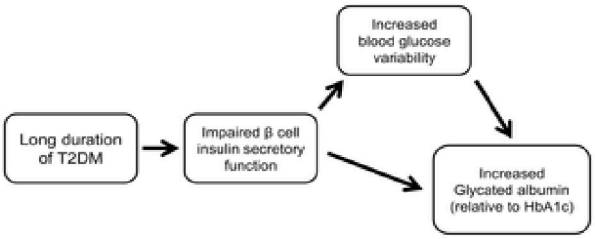

Figure a. A putative diagram of the relationship among glycated albumin, β-cell function &duration of diabetes. (33)

- HbA1c levels depend on glucose transport from plasma into erythrocytes &on intracellular glucose &protein metabolism, which indirectly reflect glycemic status. However, GA is not affected by extracellular–intracellular glucose dynamics but directly produced by the glycation process in the plasma. **(34).** GA level may not change by serum concentration of albumin, when it is calculated by the glycated proportion of total serum albumin when GA is analyzed by an enzymatic method **(30)**
- GA may reflect glucose fluctuation & postprandial glucose more sensitively than HbA1c via its role as a intermediate -term (3-week) glycemic index (**35,36**).
- Relationships between postprandial hyperglycemia &cardiovascular disease have been noted. Therefore, the correction of postprandial hyperglycemia is one of the important goals of glycemic control to prevent cardiovascular disease, the glycation speed of GA is ten times faster than HbA1c, so GA is likely to reflect the variation in blood glucose & postprandial hyperglycemia in combination with HbA1c & its value**(26).**
- levels of GA &GA/HbA1c ratios increase in subjects with poorly controlled diabetes than in subjects with well-controlled diabetes (**28**)
- GA is a superior indictor to HbA_{1c} for subjects with anemia or CKD as A1c test underestimated glycemic control when erythropoietin was used, in diabetes patients undergoing hemodialysis in Japan &the United States, while GA testing provided more accurate estimates for those patients**.(37,38).**
- GA increase compliance with testing & improve patient care &outcome, by reducing the number of recommended blood glucose tests in lieu of GA measurement, i.e., reducing the number of times people have to stick themselves from 86% to 56 % in daily SMBG testing. (**20).**
- GA represents an enormous potential saving in healthcare cost, supporting a solid economic argument regarding a shift away from more expensive glucose testing.**(20)**

2. Patients &Methods

A Cross sectional descriptive study into which Sixty-Two (62) type 2 diabetic on insulin participants were recruited at Suez Canal University hospital, aged between 25-60 years of age of either gender whose albumin and CBC indices were normal. Smokers, patients known to be CLD or DKD patients, individuals on regular ostatins, aspirin or metformin were all excluded.

Methods: Participants voluntarily proposed to join the study, they were briefed about the study by the investigator & upon their informed consent, a thorough interview for eliciting personal, socio-demographic, history clues indicative of any exclusion criteria was held, they underwent through examination & anthropometric measurements namely body mass index (BMI) was taken.

They were grouped into a non-obese group with BMI <25 Kg/m^2 & obese group whose BMI ≥25 Kg/m^2, each with a sample size of 31 participants.

Fasting Specimens were taken for FPG, HbA1c, CBC, serum albumin & PPPG was withdrawn 2 hours post prandial, all were analyzed on same day of withdrawal,while centrifused serum samples were gathered in alicots for analyzing GA & serum insulin upon delievery of kits.

Data analysis:

"IBM SPSS (Version 22) was used for data analysis & presentations. Quantitative data were presented as Mean &Standard Deviation (SD), while qualitative data were presented as frequency & percentage (%).

Differences in means between study groups were tested for statistical significance with independent-samples *t*-test. Chi-square test was used to test the statistical significance of association between categorical variables. Fisher's exact test was used as alternative to Chi-square if >20% of cells had expected values less than 5. Pearson's Correlation was used to evaluate the correlation between every two quantitative variables.

3. Results

The two groups were matched for marital status, occupation, education, maternal & paternal histories of type 2 diabetes there were no statsitically significant difference between the two groups (Table 1).

Haemoglobin level, RBC count, albumin levelswere identical and FPG & PPPG were matched for both groups with no statsitically significant difference.(Table 2)

HbA1c was slightly higher among obese while GA was lower, both with statistical insignificant difference. However, GA/HbA1c ratio was significantly low among obese compared to non-obese. Fasting insulin was significantly low among obese compared to non-obese, while the HOMA-IR showed no statistically significant difference. (Table 3).

BMI was responsible for the statistical significant difference in HbA1c between participants with &without insulin resistance. However, GA & GA/HbA1c ratio didn't differ significantly between patients with & without insulin resistance, either in obese or non-obese patients (Table 4, figures 1, 2 & 3).

Table 1. Distribution of participants in both study groups according to Socio demographic characteristics

		Non-obese (*n* = 31)		**Obese** (*n* = 31)		***p*-value**
		No.	%	No.	%	
Age groups (years)	< 40	3	9.7%	5	16.1%	0.565 [a]
	40 - <50	4	12.9%	6	19.4%	
	50 – 60	24	77.4%	20	64.5%	
	Mean ± SD (Range)	52.6 ± 8.8 (32 - 60)		50.6 ± 11.5 (25 - 60)		0.430 [c]
Gender	Male	10	32.3%	1	3.2%	**0.003 *[b]**
	Female	21	67.7%	30	96.8%	
Marital status	Single	1	3.2%	1	3.2%	0.895 [a]
	Married	24	77.4%	23	74.2%	
	Widow	4	12.9%	6	19.4%	
	Divorced	2	6.5%	1	3.2%	
Education	Illiterate	10	32.3%	8	25.8%	0.945 [b]
	Read & write	6	19.4%	7	22.6%	
	Primary/ Preparatory	7	22.6%	9	29.0%	
	Secondary/equivalent	5	16.1%	5	16.1%	
	University/ Postgrad.	3	9.7%	2	6.5%	
Occupation	Housewife	16	51.6%	20	64.5%	0.892 [a]
	Manual/unskilled workers	8	25.8%	6	19.4%	
	Skilled worker	2	6.5%	2	6.5%	
	Professional	2	6.5%	1	3.2%	
	Retired	3	9.7%	2	6.5%	
Family History of Type II DM	Maternal	13	41.9%	13	41.9%	1.00 [b]
	Paternal	5	16.1%	11	35.5%	0.082 [b]
Duration of DM (years)	<10	8	25.8%	13	41.9%	0.180 [b]
	≥10	23	74.2%	18	58.1%	
	Mean ± SD (Range)	13.4 ± 8.3 (0.4 - 30)		10.7 ± 8 (0.1 - 30)		0.196 [c]

*. Statistically significant at p<0.05; [a]. Fisher's Exact test, [b]. Chi-square test, [c]. Independent samples *t* test

Table 2. Distribution of participants in both study groups according to laboratory characteristics

	Non-obese (*n* = 31)		**Obese** (*n* = 31)		***p*-value**
	Mean	±SD	Mean	±SD	
FPG	200.2	98.5	227.1	100.4	0.291
PPPG	267.7	127.2	295.5	121.7	0.382
Hb (mg/dl)	12.6	1.2	12.0	1.0	0.052
RBCC (^6)	4.5	0.5	4.6	0.7	0.467
Albumin	4.0	0.5	4.0	0.5	0.874

*. Statistically significant at p<0.05; Independent Samples *t* test

**. Statistically significant at p<0.01; Independent Samples *t* test

Table3. Distribution of participants in both study groups according to glycemic indicators characteristics

	Non-obese (*n* = 31)		**Obese** (*n* = 31)		***p*-value**
	Mean	±SD	Mean	±SD	
HbA1c	9.0	2.3	9.6	2.5	0.342

GA	600.0	174.3	579.3	162.6	0.631
GA/ HbA1C ratio	66.8	9.9	61.1	11.2	**0.040***
Fasting Insulin	32.1	27.2	21.1	11.7	**0.044***
HOMA-IR	6.7	14.8	4.0	2.5	0.313

*. Statistically significant at p<0.05; Independent Samples *t* test
**. Statistically significant at p<0.01; Independent Samples *t* test

Table 4. Comparing laboratory Markers for glycemic control between participants with/without insulin resistance stratified by BMI

	Obesity (BMI)	**Insulin Resistance** (HOMA-IR)				***p*-value**
		No (*n* = 33)		**Yes** (*n* = 29)		
		Mean	±SD	Mean	±SD	
HbA1c	Non-obese	8.4	2.2	9.7	2.4	0.122
	Obese	8.6	2.0	10.8	2.5	**0.013***
GA	Non-obese	565.0	190.3	637.4	153.0	0.255
	Obese	550.0	148.2	615.0	177.5	0.276
GA/ HbA1C ratio	Non-obese	66.7	9.1	66.9	11.0	0.965
	Obese	64.1	9.0	57.6	12.8	0.108

*. Statistically significant at p<0.05; Independent Samples *t* test

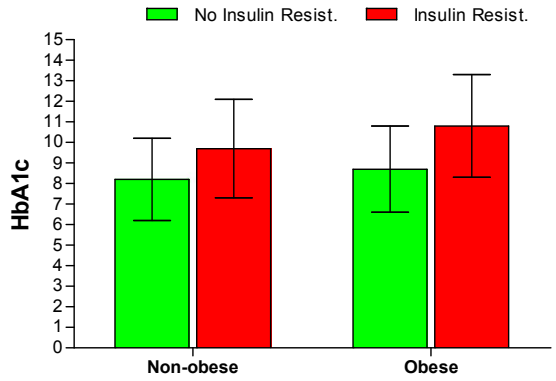

Figure 1. Comparing mean HbA1c between patients with/without insulin resistance stratified by BMI

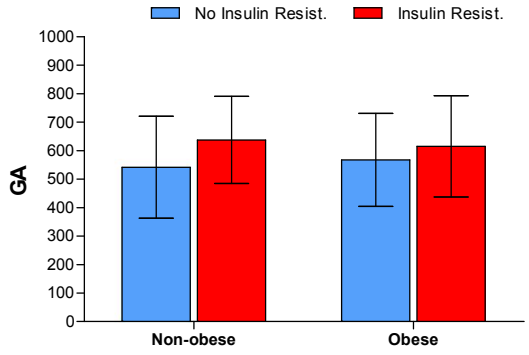

Figure 2. Comparing mean GA between patients with/without insulin resistance stratified by BMI

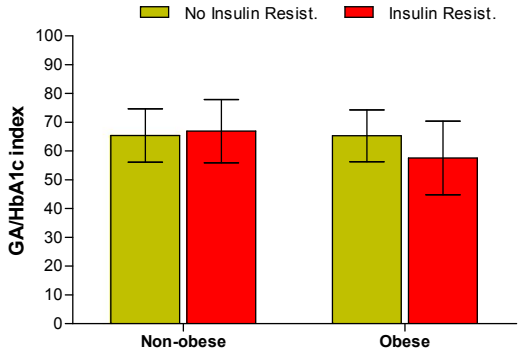

Figure 3. Comparing mean GA/HbA1c ratio between patients with/without insulin resistance stratified by BMI

4. Discussion

As more than 80% of diabetes deaths occur in low &middle income countries, WHO projects that diabetes will be the 7th leading cause of death in 2030. **(1)** In 2012 Egypt was ranked as the 8th top country with people with diabetes with 16.62%, while world's diabetes comparative prevalence is 8.30 % **(2).**

Monitoring of glycemic status, as performed by patients &health care providers, is a cornerstone of diabetes care &prevention of diabetes complications.

Although unknown influences on GA or HbAlc may exist. among various glycated proteins, serum GA has been reported to be a useful &rapid marker for monitoring short-term variations of glycemic control during treatment of diabetic patients since the turnover of serum albumin is much shorter(half –life of 17 days) than that of HbA1c **(39)**.

This Cross sectional study was designed aiming at assessing the correlation of each of glycated albumin and glycated haemoglobin to BMI and

HOMA-IR in type 2 diabetic patients via the hypothesis of negative correlation between adiposity & glycated albumin.

None of the 62 participants-aged between 25-60 years -who consented to join the study was smoker, CLD or DKD patient, was receiving regular metformin, statin or NSAIDs therapy.

Regarding glycemic control, comparing of fasting & postprandial plasma glucose levels among both groups revealed that:

Though FPG was higher (227.1 mg/dL ±100.4 in obese group compared to non-obese (200.2±98.5) & PPPG was higher (295.5 ± 121.7 mg/dL) in obese group as well, than non-obese group (267.7 ± 127.2 mg/dL) yet neither of them was of statistically significant difference (*P* value =0.291 &0.382 respectively).

Similarly, HbA1c was slightly higher among obese (9.6 % ± 2.5) compared to non-obese (9.0 % ± 2.3) with no statistically significant difference. (P value >0.005).

The aforementioned results were in agreement with **Koga *et al.* (2006)** who studied 209 diabetic patients &found that HbA1c levels didn't correlate to BMI **(40).** Also in a study of 107 individuals with type 2 diabetes without advanced complications; HbA1c level and BMI showed very weak correlation ($r = -0.04$; $p = 0.65$).**(41)**

Daousi *et al.* (2006) showed that there was a trend towards poorer glycaemic control (higher HbA1c levels) with increasing BMI which was statistically significant in men but not in women **(42),**which wasn't in agreement with this study results.

The current study hypothesized the existence of negative correlation between BMI &glycated albumin, & this was elicited by:

- The lower measurements of glycated Albumin (GA) among obese participants (579.3 ± 162.6 µmol/L) than in non-obese ones (600.0 ± 174.3 µmol/L), though the difference was statistically insignificant (*P* value = 0.631).
- lower GA/HbA1c ratio among obese participants (61.1 ±11.2) compared to non-obese (66.8 ± 9.9) was statistically significant (*P* value = 0.044).

The previous results were in agreement with **Koga** *et al.* **(2006)** who studied the effects of BMI on GA measurement in 209 diabetic patients & showed that BMI had a significant negative correlation on GA levels as well as ratio of GA to HbA1c **(40).** Another study investigated the effect of obesity on GA levels in type 2 DM and proved a significant negative correlation ($r = -0.28$; $p = 0.004$) as the GA of the obese group in that study was significantly lower than those in the non-obese group.**(41).**

Fasting insulin was significantly (P value <0.005) lower (21.1 ± 11.7 mg/dL) among obese participants compared to non-obese (32.1± 27.2 mg/dL) while the HOMA-IR showed a difference which was not statistically significant difference (*P* value >0.005), this is in disaggrement with **Weyer** *et al.* **(2001)** who found higher hyperinsulinemia associated with increasing BMI in different Caucasian and Pima Indian populations**(43)**, role of insulin therapy may be implicated in this study.

In the current study, Glycemic markers HbA1c, GA, & GA/HbA1c ratio were compared to insulin resistance in obese &non -obese & it was found that HbA1c had a statistically significant (P value = 0.013) higher difference in obese with insulin resistance (10.8% ±2.5) compared to obese with no insulin resistance (8.6± 2.0%)

Even HbA1c levels were lower in non-obese either with or without insulin resistance though these weren't statistically significant (8.4% ± 2.2 & 9.7 % ± 2.4 respectively, *P* value=0.122).

Though none were statistically significant (*P* > 0.05), yet the inverse relationship between GA & BMI was emphasized as GA was lower in obese with &without insulin resistance (615 µmol/L ± 177.5 & 550.0±148.2 µmol/L respectively) compared to GA in non-obese with &without insulin resistance (637.4 ± 153.0 µmol/L & 565.0 ± 190.3 µmol/L respectively) & GA/HbA1c ratio was lower in obese with &without insulin resistance (57.6 ± 12.8 & 64.1 ± 9.0 respectively) compared to GA/HbA1c ratio in non-obese with & without insulin resistance (66.9 ± 11.0 & 66.7 ± 9.1 respectively). This might be explained by the presence of inflammatory markers associated with obesity & T2DM (**18, 44)** which apparently influence levels of GA.

Conclusion

This study showed that GA and GA/HbA1c ratio are lower in type 2 DM patients with BMI ≥ 25 Kg/m^2 and GA is lower in obese type 2 DM with insulin resistance than obese with no insulin resistance and also lower than non-obese with insulin resistance, so the current analysis demonstrated a need of prudent evaluation of GA values in obese diabetic patients in office practice.

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