Correlation between Glycated Hemoglobin (HBA1c), Glycated Albumin Levels and Cardiovascular Risk Factors in Pre-Diabetic Metabolic Syndrome Patients

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Abstract

Background: The metabolic syndrome is a major and escalating public-health problem. It is a predisposing factor of cardiovascular disease. Cardiovascular disease is a leading cause of morbidity and mortality all over the world. Studies have shown that subjects having pre-diabetes are also at a high risk for CVD. Pre-diabetes refers to an intermediate stage between normal glucose tolerance and overt T2DM. Glycated albumin reflects short-term (2-3 weeks) mean glycemic levels. GA values, unlike HbA1c, are not affected by changes in erythrocyte lifespan.

Aim of Study: The aim of the study is to correlate between HbA1c, glycated albumin and cardiovascular risk factors in prediabetic metabolic syndrome patients.

Patients and Methods: One hundred pre-diabetic patients diagnosed as metabolic syndrome were subjected to full history taking and examination, full anthropometric measurements, laboratory tests including: FBS, uric acid, HbA1c, lipid profile, glycated albumin levels, urea, creatinine and A/c ratio.

Results: Our study showed that anthropometric measures including weight, waist circumference, neck circumference, hip circumference, triceps thickness were all negatively correlated to glycated albumin with p-values (<0.001, 0.003, <0.001, 0.007, 0.014) respectively. On the other hand, weight, waist circumference, neck circumference and subscapular skin fold thickness were positively correlated to HbA1c levels with p-values (<0.001, 0.01, 0.016 and 0.009) respectively.

Regarding metabolic syndrome and cardiovascular risk factors, triglyceride levels are negatively correlated to HbA1c levels (p-value 0.01). LDL levels are positively correlated to HbA1c levels (p-value 0.02). BMI is negatively correlated to glycated albumin level (p-value <0.001) but positively correlated to HbA1c level (p-value <0.001). As for pre-diabetes, fasting blood sugar is positively correlated to glycated albumin levels (p-value 0.002) with no statistical correlation to HbA1c levels.

Conclusion: Both glycated albumin and HBA1c are correlated to anthropometric measures hence their importance in assessment of obesity. HbA1c is more correlated to metabolic syndrome and cardiovascular risk factors than glycated albumin. Glycated albumin showed positive correlation to FBG, thus can be used for diagnosis of pre-diabetes especially when combined with HbA1c.

Key Words: Metabolic syndrome — HbA1c — Glycated albumin — Cardiovascular risk factors — Pre-diabetes.

Introduction

THE metabolic syndrome (MetS) is a major and escalating public health problem and clinical challenge worldwide in the presence of urbanization, surplus energy intake, increasing obesity, and sedentary life habits. MetS confers a fivefold increase in the risk of type 2 diabetes mellitus (T2DM) and twofold the risk of developing cardiovascular disease (CVD) over the next 5 to 10 years [1].

A subject has the MetS if he or she has three or more of the following criteria: Abdominal obesity: WC -102cm in men and -88cm in women, Hypertriglyceridemia: -150mg/dl, Low HDL-C: <40mg/dl in men and <50mg/dl in women, High blood pressure (BP): >130/85mmHg, High fasting glucose levels: >110mg/dl [2].

Cardiovascular disease is a leading cause of morbidity and mortality all over the world. Studies have shown that subjects having pre-diabetes are also at a high risk for CVD [3].

Pre-diabetes is a condition that precedes diabetes and it is diagnosed according to American Diabetes Association (ADA) by the following criteria: Impaired Fasting Glucose (IFG) is defined as Fast-
Glycated albumin (GA) is a ketoamine, which is formed by non-enzymatic glycation of serum albumin. It reflects short-term (2-3 weeks) mean glycemic levels [5]. GA values are not affected by changes in erythrocyte lifespan, and measurement of GA is not influenced by anemia or other conditions which invalidate HbAlc measurements in the diagnosis of diabetes [5].

HBA1c combined with glycated albumin improves detection of pre-diabetes. Studies have found that glycated albumin can identify pre-diabetes not detected by HbAlc [6].

Many studies have shown strong positive correlation between HbAlc levels and existing CVDs risk factors. Also many studies presented HbAlc as an independent predictor of cardiovascular risk [7]. On the other hand, studies showing the role of glycated albumin in assessing the cardiovascular risk in pre-diabetic metabolic syndrome patients are lacking, which is a field requiring further studies.

**Material and Methods**

The study is a cross sectional observational study that was designed to analyze data from 100 Egyptian patients with metabolic syndrome based upon the American Heart Association 2004 guidelines for diagnosis of metabolic syndrome and Pre-diabetes diagnosed by ADA guidelines and age ranging from 18-50 years.

All patients were chosen from internal medicine department, endocrinology, nutrition and diabetes outpatient clinic in Kasr El Aini teaching Hospital of Cairo University from August 2019 to August 2020.

Patients were recruited according to the following inclusion criteria: Egyptian patients, aged from 18 to 50 years, fulfilling the criteria of metabolic syndrome, with documented lab evidence of pre-diabetes.

Metabolic syndrome was defined as any 3 out of the following: Abdominal obesity: WC -102cm in men and 88cm in women; Hypertriglyceridemia: >150mg/dL; Low HDL-C: <40mg/dL in men and <50mg/dL in women; High blood pressure (BP): >130/85mmHg; High fasting glucose: >110mg/dL [2].

Pre-diabetes was defined by the following criteria: Impaired Fasting Glucose (IFG): Defined as fasting blood glucose levels between 100 and 125mg/dL; Impaired oral glucose tolerance test (OGTT); defined as plasma glucose 2 hours after ingestion of 75-g OGTT levels ranging between 140 and 199 mg/dL; HbAlc level from 5.7 to 6.4% [4].

Exclusion criteria were: Patients younger than 18 years or older than 50 years, anemia, chronic liver disease, chronic kidney disease, thyroid disease, malignancy and heart failure.

All patients signed a written informed consent after detailed explanation of study procedure, expected risks, and anticipated benefits. All the patients were subjected to detailed history taking and clinical examination. Anthropometric measures were done to assess the degree of obesity and fat distribution in the study group.

Body weight and Height were measured in light clothing and without shoes to the nearest 0.5kg, using calibrated scales.

BMI was calculated as weight (kg) divided by height squared (m²): (Weight (kg))/ (Height in meters)². It is classified as overweight (BMI 25-29.9), class I obesity (BMI 30-34.9), class II obesity (BMI 35-39.9) and class III obesity (BMI-40) [8].

Waist circumference was measured in cm, between the lower rib margin and the iliac crest, with subjects standing with their heels together, during normal expiration with a non-stretchable measuring tape, measures >88 cm in females and >102 cm in males are considered one of the criteria of metabolic syndrome.

Sub-scapular skin fold thickness was measured in mm, it is picked up just under the lower angle of the scapula.

Neck circumference is measured in cm, was measured from the level just below the laryngeal prominence perpendicular to the long axis of the neck, it is a potentially useful initial screening tool for overweight/obesity. A neck circumference > or = 35.5cm in men and > or = 32cm in women should be considered the cutoff point for overweight/obesity [9,10].
Laboratory tests including: FBS, HbAlc, lipid profile, glycated albumin levels, urea, creatinine, uric acid and A/c ratio were withdrawn for all patients. For measurement of glycated Albumin, the kit is composed of GSP Assay and Albumin Assay. The GSP Assay uses proteinases to digest serum proteins including glycated protein molecules into low molecular weight glycated protein fragments (GPF), and uses Fructosaminase, a microorganism originated amadoriase to catalyze the oxidative degradation of Amadori product GPF to yield protein fragment (PF), glucosone and H2O2. The suggested upper limit of the nondiabetic range of glycated Albumin can vary between 10.4% to 15.7% [11].

Fasting lipid profile by which patient is considered having dyslipidemia if serum cholesterol >200 mg/dL, triglycerides >150 mg/dL. Albumin creatinine ratio was measured by dividing urinary albumin in mg/L by urinary creatinine in gm/L in spot urine sample: Normo-albuminuria with ACR: <30 mg/gm creatinine, moderately increased albuminuria with ACR 30-300 mg/gm creatinine, and severely increased albuminuria (macro-albuminuria) with ACR >300 mg/gm creatinine.

Ethical consideration:
Study protocol and informed consent were submitted for Institutional Review Board and Ethical Committee at The Internal Medicine Department of Cairo University and approval was granted on 8.12.2019 with the acceptance Code: MS-224-2019.

Statistical analysis:
All data was entered into a Microsoft Excel sheet. Statistical analysis of data was done by IBM computer using SPSS (statistical program for social science version 21). Description of quantitative variables was expressed as mean, standard deviation (SD), Median and iqr. Description of qualitative variables was expressed as number and percentage. Chi-square test was used to compare qualitative variables between groups. Fisher exact test was used when one expected cell or more are less than 5. Mann Whitney test was used instead of unpaired t-test in non-parametric data (SD >30% mean). Kruskal wallis test used instead of one wayanova in non-parametric data (SD >30% mean). Regression analysis was done to calculate correlation coefficients with greater accuracy and probable causal relationships. p-value >0.05 insignificant, p<0.05 significant, p<0.01 highly significant [12].

Results
A full set cross sectional observational study was designed to analyze data from 100 (88 females and 12 males) Egyptian patients with metabolic syndrome. The patients' age ranges from 27 to 50 years with mean value 38.2±8.03 years and median 39 years.

![Graph showing correlation between Glycated albumin and Hip circumference.](attachment:graph.png)
Fig. (2): Showing correlation between glycated albumin and Triceps skin fold: There is a negative statistical correlation between Glycated albumin and Triceps skin fold (p-value: 0.014).

Regarding metabolic syndrome variables, Triglyceride levels are negatively correlated to HbAlc levels (p-value 0.01). LDL levels are positively correlated to HbAlc levels (p-value 0.02). Regarding pre-diabetes, fasting blood sugar is positively correlated to glycated albumin levels (p-value 0.002) with no statistical correlation to HbAlc levels.

Among the cardiovascular risk factors, BMI is negatively correlated to glycated albumin level (p-value <0.001) but positively correlated to HbAlc level (p-value <0.001).

There is no significant statistical correlation between glycated albumin and HbAlc levels.

Table (4): Showing correlation between HbAlc, glycated albumin and metabolic syndrome variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Glycated Albumin r</th>
<th>p-value</th>
<th>HbAlc r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS</td>
<td>0.307</td>
<td>0.002</td>
<td>0.082</td>
<td>0.417</td>
</tr>
<tr>
<td>TG</td>
<td>0.128</td>
<td>0.203</td>
<td>-0.258</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL</td>
<td>0.167</td>
<td>0.097</td>
<td>-0.154</td>
<td>0.126</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.032</td>
<td>0.751</td>
<td>0.029</td>
<td>0.777</td>
</tr>
<tr>
<td>LDL</td>
<td>-0.006</td>
<td>0.956</td>
<td>0.233</td>
<td>0.02</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.102</td>
<td>0.312</td>
<td>0.041</td>
<td>0.684</td>
</tr>
</tbody>
</table>

Fig. (4): Showing correlation between FBS and glycated albumin: Glycated albumin positively correlates to FBS (p-value 0.002).

Fig. (5): Showing correlation between HbAlc and triglycerides (TG): HbAlc negatively correlates to triglycerides (p-value 0.01).

Fig. (6): Showing correlation between HbAlc and LDL levels: HbAlc positively correlates to LDL levels (p-value 0.02).
Table (5): Correlation between cardiovascular risk factors and glycated albumin and HbAlc.

<table>
<thead>
<tr>
<th></th>
<th>Glycated Albumin</th>
<th>HbAlc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>0.037</td>
<td>0.713</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.376</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.085</td>
<td>0.237</td>
</tr>
<tr>
<td>FBS</td>
<td>0.307</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex</td>
<td>0.25</td>
<td>0.799</td>
</tr>
</tbody>
</table>

Fig. (7): Showing correlation between HbAlc and BMI: There is a highly significant positive statistical correlation between HbAlc and BMI (p-value <0.001).

Fig. (8): Showing correlation between glycated albumin (GA) and BMI: A negative statistical correlation between GA and BMI (p-value <0.001).

Table (6): Shows no correlation between HbAlc and glycated albumin levels.

<table>
<thead>
<tr>
<th></th>
<th>HbAlc</th>
<th>Glycated Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p-value</td>
</tr>
<tr>
<td>HbAlc</td>
<td>—0.07</td>
<td>0.492</td>
</tr>
<tr>
<td>Glycated Albumin</td>
<td>—0.07</td>
<td>0.492</td>
</tr>
</tbody>
</table>

Fig. (9): Showing statistical correlation between HbAlc and glycated albumin levels: No statistical correlation between both.

Discussion

The metabolic syndrome (MetS) is a major and escalating public-health problem and confers a 5-fold increase in the risk of type 2 diabetes mellitus (T2DM) and 2-fold the risk of developing cardiovascular disease (CVD) over the next 5 to 10 years [1].

Thus, our study aim is to correlate glycated albumin and HbAlc levels and cardiovascular risk factors in pre-diabetic metabolic syndrome patients. We correlated the levels of both glycated albumin and glycated hemoglobin with anthropometric measures, metabolic syndrome related variables and cardiovascular risk factors variables.

Regarding anthropometric measures, our study showed negative correlation between BMI and glycated albumin levels (p-value <0.001) but positive correlation between BMI and HbAlc levels (p-value <0.001) which is cemented by various studies.

This expectedly agrees with many previous studies like the study of Wen et al. They conducted a study on 3976 subjects which concluded that glycated albumin levels has a negative correlation to BMI, (p-value <0.001) and HbAlc has a positive correlation to BMI (p-value <0.001) [13]. Also, a study from Japan demonstrated that BMI was an independent negative risk factor for GA in 212 non diabetic individuals (p-value <0.0001) [14].

Moreover, a study was conducted on 2562 patients who received an oral glucose tolerance test at the hospital in Shanghai. The levels of GA were independently and negatively correlated with BMI regardless of diabetes status. For each 1kg/m$^2$ increase in BMI, the value of GA was reduced by approximately 0.13% [15].

The detailed mechanisms behind the inverse relationship between central obesity and GA are not well understood. Recent studies have suggested that inflammation may play an important role. Obesity is chronic low-grade inflammatory disease state.
Inflammation reduces the rate of albumin synthesis and increases its rate of catabolism, which ultimately leads to decreased level of serum albumin hence low level of glycated albumin in obese people [14].

On the contrary, Miyashita et al. [16] indicated that obese children had higher serum ALB than non-obese children. Koga et al. [14] found no correlation between BMI and ALB concentrations in a study conducted on 228 Japanese subjects. Also, Yoshiuchi et al. [17] conducted a study on 163 patients, 93 of them type 1 DM and 75 of them type 2 DM which failed to find any correlation between Glycated albumin and BMI.

In our study, waist circumference was negatively correlated to glycated albumin level (p-value 0.003), but was positively correlated to HbAlc level (p-value 0.01).

In agreement with our study, a study conducted on 1799 patients stated that waist circumference is positively correlated to HbAlc (p-value <0.001) and negatively correlated to glycated albumin (p-value 0.03) [18]. This was also supported by Wang F et al. [19] in a study carried on 2563 patients with normal glucose tolerance test that revealed that Glycated albumin is negatively correlated to waist circumference (p-value 0.001).

Another finding in our study is Hip Circumference showing negative correlation to glycated albumin (p-value 0.007) and no correlation to HbAlc level.

Agirbasli et al. [20] stated that hip circumference is a good predictor for metabolic syndrome in children with (p-value 0.009). Also, across-sectional study involved 405 diabetic stated that hip circumference appears to be a potential predictor of visceral fat estimate among type 2 diabetes patients, which reflects increased cardiovascular risk [21]. Unlike our study, a study on 111 subjects, stated that HbAlc was weakly correlated to hip circumference (p-value 0.326) [22].

On the other hand, Wisgerhof et al. [23] found independent and opposite associations of waist and hip circumferences with HbAlc. Larger waist circumference and smaller hip circumference have previously been shown to be associated with risk for developing type 2 diabetes, independent of BMI.

Our study showed that neck circumference is negatively correlated to glycated albumin level (p-value <0.001), but it is positively correlated to HbAlc level (p-value 0.016).

In a meta-analysis of observational studies by Saneei et al. [24], Neck circumference was positively correlated to HbAlc; although further investigations with prospective design are required to confirm these findings Borel et al. [25].

Found in a study carried on 305 obese patients that neck circumference was the only marker significantly associated with all cardio metabolic risk markers. Also Zhou et al. [26].

Stated that neck circumference measurement is a simple and effective anthropometric index to predict metabolic syndrome with cut-off value of -37cm in males and -33cm in females among the population of China. On the other hand Joshipura et al. [27].

Stated that neck circumference can be used instead of waist circumference and BMI in anthropometric measures and it has no significant correlation to HbAlc (p-value 0.28). Our study showed that Triceps skin fold thickness is negatively correlated to glycated albumin (p-value 0.014) and no significant statistical correlation to HbAlc level. Moreno et al. [28].

Stated that Triceps skin fold is a good predictor for metabolic syndrome in children. Also, Ruiz-Alejos et al. [29].

In a study suggested that skin fold thickness, if used as part of routine assessments, might improve the detection process of T2DM and Hypertension.

On the other hand, in Canada a study was done on 7605 participants to compare the use of skin fold measurement and the use of BMI and waist circumference in predicting health risk, stated that BMI refined by WC is related to health risk in the general population. Additionally, Skin fold thickness does not appear to add information to BMI and WC, and it has poor reliability [30].

Regarding metabolic syndrome, our study showed no significant correlation between Hypertension and both glycated albumin and HbAlc. Fukoka et al. [31].

Supported this conclusion in a study conducted on 98 patients ESRD patients with diabetic nephropathy showed that systolic BP and diastolic BP were not correlated to neither HbAlc nor glycated albumin. However, other studies stated that hypertension is positively correlated to HbAlc (p-value <0.001) but it has no correlation to glycated albumin [13,32].

Also, Norimatsu et al. [33] in a study carried on 244 consecutive patients reported that Hypertension and GA levels were independent predictors of the presence of coronary artery disease (CAD) in all patients. Although GA was not a significant predictor in the non-DM group, glycated albumin may be superior to HbAlc as a marker for evaluating the presence of CAD.

In our study, Triglycerides levels are negatively correlated to HbAlc levels (p-value 0.01) with no statistical correlation to glycated albumin levels.
Tenebaum et al. [34] emphasized that hypertriglyceridemia has been a long unfairly neglected major cardiovascular risk factor. In agreement with our study, Pu et al. [35] stated that there is no significant statistical correlation between GA and triglycerides. Also, Maruo et al. [36] stated that GA has no correlation to triglycerides in a study conducted on 123 patients.

On the contrary, Sarkar S and Meshram A conducted a study which showed no correlation between HbAlc and triglycerides [37]. Also, Wen et al. [13] stated that triglycerides are positively correlated to HbAlc (p-value 0.001) and negatively correlated to glycated albumin (p-value 0.001).

Another important finding in our study was that LDL levels are positively correlated to HbAlc (p-value 0.02) but showed no significant correlation between LDL and glycated albumin.

Kidwai et al. [38] examined 142 patients with type 2 diabetes mellitus and concluded that there is positive statistical correlation between HDL and LDL levels (p-value <0.05). Also, Chan et al. [39] in a study on 517 subjects stated that LDL levels are positively correlated to HbAlc levels. Moreover, Pu et al. [35] stated that there was no statistical correlation between LDL levels and glycated albumin levels.

On the contrary, Furusyo et al. [5] conducted a study on 1575 person which showed that LDL levels are negatively correlated Glycated albumin and no significant correlation between HbAlc and LDL levels.

Our study showed there were no significant correlation between both Glycated albumin and HbAlc levels and total cholesterol or HDL levels.

In agreement with our study, Sarkar et al. [37], in a study involved 60 patients, stated that HbAlc is not related to total cholesterol levels. Also Alzahraeni et al. conducted a study involved patients showed that HbAlc levels has no significant correlation with HDL levels [40].

Furusyo et al. [5] stated that cholesterol levels are positively correlated to both GA and HbAlc (p-value 0.013 and <0.001 respectively) and HDL Levels are negatively correlated to both GA and HbAlc (p-value 0.009 and 0.005 respectively).

Regarding pre-diabetes our study showed that FBS was positively correlated to Glycated albumin (p-value 0.02) but there was no significant statistical correlation with HbAlc.

In 2008 Yoshiuchi et al. [17] conducted a study on 163 patients, 93 of them type 1 DM and 75 of them type 2 DM which showed that Glycated albumin was positively correlated with FBS in both Type 1 DM and type 2 DM (p-value 0.002, 0.0001 respectively) but HbAlc was correlated to FBS in Type 1 DM (p-value <0.0001) but not in type 2 DM.

Sumner et al. [41] conducted a study on 236 African obese and non obese immigrant participants, found that in non obese patients glycated albumin is a better diagnostic test especially when combined with HbAlc for prediction of pre-diabetes.

Xu et al. [18] stated that glycated albumin is more convenient to use in clinical practice owing to the reasonable evidence that non fasting measurements of GA levels could be employed for diabetes screening as well due its short half life and its correlation to plasma glucose levels.

On the other hand Bazyar et al. [42] showed in a study that HBA1c correlates positively with FBS in Type 2 DM (p-value 0.001).

Our study showed that Creatinine level is positively correlated to glycated albumin level (p-value 0.005) and negatively correlated to HbAlc (p-value 0.004).

Inaba et al. [43] conducted a study on538 HD patients with type 2 diabetes, 828 HD patients without diabetes, and 365 patients with type 2 diabetes and normal renal function, it showed a negative correlation between serum creatinine and HbAlc (p-value 0.04, 0.48 and 0.45 respectively) but no significant statistical correlation between glycated albumin and serum creatinine levels.

However, a study conducted on 307 diabetic subjects of whom 258 were on hemodialysis and 49 were without overt renal disease, failed to show a significant statistical correlation between serum creatinine and HbAlc or glycated albumin [44].

Our study showed that A/C ratio is positively correlated to HbAlc levels (p-value <0.001) with no correlation to glycated albumin levels.

A study conducted on 238 patients with type 2 diabetes and found that HbAlc variability is strongly associated with the development of macroalbuminuria, especially patients under a microalbuminuria state (p-value <0.001) [32]. Also, a prospective cohort study in Taiwan found that variability in HbAlc levels is a risk factor for the development of microalbuminuria [45].

On the other hand, Yoon et al. [46] in a study on 154 participants with a median follow-up of 2.8 years were enrolled in this retrospective longitudinal study, stated that Mean GA levels, rather than mean HbAlc levels, are more closely associated with the progression of diabetic nephropathy.

Finally, our study showed no significant statistical correlation between HbAlc levels and glycated albumin levels in pre-diabetic metabolic syndrome patients.
Zeng, Y. et al. [47] conducted a study on 3,414 participants which agreed with our finding that HbAlc and GA values are inconsistent in the population they studied.

On the contrary; Bellia et al. [48] conducted a study which included 334 consecutive subjects, and found that GA was significantly correlated with HbAlc (r=0.31; p<0.0001). Also, Inaba et al. [43] reported a significant positive correlation between GA and HbAlc in their HD group (r=0.777, p<0.001). Their study involved 538 HD patients with type 2 diabetes.

Moreover; Kitajima, Y et al. [49] in a study conducted on 133 diabetic patients undergoing hemodialysis, it showed a significant positive correlation was observed between GA and HbAlc levels (r=0.562, p<0.0001).

To summarize: Both glycated albumin and HbAlc are correlated to anthropometric measures hence their importance in assessment of obesity. HbAlc is more correlated to metabolic syndrome and cardiovascular risk factors than glycated albumin. Glycated albumin showed positive correlation to FBG, thus can be used for diagnosis of pre-diabetes especially when combined with HbAlc.

References


Risk Factors in Pre-Diabetic Metabolic Syndrome Patients


