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Research Article

Identifying the Relation between Fasting Blood Glucose and Glycosylated Haemoglobin Levels in Greek Diabetic Patients

Abstract

Introduction: Diabetes Mellitus (DM) is associated with long-term damage, dysfunction, and failure of various body organs. Glycosylated haemoglobin (GHbA1c) is a significant biochemical marker in patients with DM which provides an estimation of long-term average glycaemia. The aim of this study was to evaluate the relation between fasting serum glucose (GLU) level and GHbA1c in DM patients and healthy controls, to evaluate the differences between male and female patients and to evaluate the correlation between estimated Average Glucose (eAG) and GLU.

Materials and Methods: The study included 800 DM patients (448 male, 352 female), and 200 (100 male, 100 female) healthy control patients. We used statistical modeling and analysis to evaluate the data.

Results: Via linear regression we found statistically significant linear relations between GLU and GHbA1c for female and male patients, male patients had higher mean level of GLU than female (+10.7mg/dL $p<0.05$), similarly for GHbA1c (+0.24% $p<0.05$). For healthy controls, neither linear relation nor gender difference was identified. Subsequently we calculated eAG on the basis of GLU level, we found a significant correlation (Corr.Coeff.=0.56) between GLU and eAG for DM patients and no correlation (Corr.Coeff.=0.026) for healthy controls. These findings were consistent when the analysis was repeated separately for both genders, however with no difference between men and women.

Conclusions: eAG and GLU values cannot be used in general population interchangeably. One strategy option could be the use of eAG levels together with GHbA1c values.

Introduction

Diabetes mellitus (DM) is a metabolic disorder which is characterized by a defect of normal glucose metabolism resulting in chronic hyper glycaemia and disturbances of carbohydrate, fat and protein metabolism [1]. DM constitutes a major public health problem requiring global attention because it is associated with long-term damage, dysfunction, and failure of various body organs, especially the eyes, kidneys, nerves, heart and blood vessels [2-4]. The prevalence of DM has been increasing steadily worldwide and is estimated to grow to 4.4% by 2030, while type 2 DM is accounting for the 95% of prevalence among patients with diabetes [2-5]. In Greece, there is a considerable increase of 1% in the prevalence of DM annually, attributed to decreasing levels of physical activity, increasing obesity rates, population ageing, lifestyle habits and unhealthy dietary behaviors [6,7]. Glycosylated haemoglobin (GHbA1c) was identified as an unusual haemoglobin in patients with diabetes many years ago and its significance in relation to diabetes was first appreciated by Rahbar et al. [8], GHbA1c is formed through the non-enzymatic binding of circulating glucose to hemoglobin, a process called glycation. The rate of formation of GHbA1c is directly proportional to the ambient glucose concentration. Since glycation occurs over the entire red blood cell life span, GHbA1c can be interpreted as an index of average blood glucose over the preceding

two months [9,10]. GHbA1c measurement provides an objective and quantitative estimation of long-term average glycaemia and it is recommended for checking glycaemic control in people who might be a pre-diabetic stage, for documenting the degree of glycaemic control at initial assessment and for monitoring glycaemic control in diabetic patients, in order to reduce the risks associated with the development and progression of chronic DM complications [10-12]. GHbA1c measurement is also being used increasingly by quality assurance programs to assess the quality of diabetes care [13] and to identify diabetic from healthy population [14]. The International Expert Committee on the role of GHbA1c in DM recommended the use of a GHbA1c level of 6.5% or higher to diagnose type 2 DM [15,16]. Since GHbA1c results can vary considerably when measured by different laboratories or analytical methods, many studies and trials have been realized for the measurement and the standardization of the assay, in order to develop international harmonization and make the results reported from different laboratories comparable [16,17]. The relationship between the average blood glucose level and the GHbA1c level has been investigated in many studies. The ADAG Study Group concluded that GHbA1c could be reliably translated into estimated average glucose (eAG). For this purpose the group developed the following linear regression equation, which was derived from adults with type 1 and type 2 DM, as well as control subjects: eAG (in mg/dL)

= $28.7 \times A1C - 46.7$ [18-20]. The major advantage of using eAG for chronic glycaemia is that it is expressed with the same measurement units as acute glycaemia, offering patients a better understanding of their GHbA1c results when they correlate them to their daily glucose measurements [21]. Even though the aforementioned equation was recommended by the American Diabetes Association, a significant debate continues, based mostly on concerns about the population studied by the ADAG study, on which the equation is based [22,23].

The aim of this study was a) to evaluate the relation between fasting serum glucose (GLU) level and GHbA1c both in diabetic patients and healthy controls, b) to evaluate the differences between diabetic patients and healthy controls, c) to evaluate the differences between male and female patients and d) to evaluate the correlation between eAG and GLU.

Materials and Methods

The population of this prospective study included 800 type 2 diabetic patients, 448 (56%) male and 352 (44%) female, aged between 32 and 70 years. Patients were recruited from the Internal Medicine Department, during a three year period of time. The diagnosis of DM was based on the American Diabetes Association criteria for type 2 DM (fasting plasma glucose level higher than 126 mg/dL and/or glucose level exceeding 200 mg/dL at 2 hours in the 75 g oral glucose tolerance test).

All patients were having minimum diabetic duration of one year and hemoglobin levels between 12 and 16 g/dL. Patients with conditions that affect the mean life of erythrocytes (such as haemolysis, blood loss and hemoglobinopathies) were not included in this study. The controls incorporated in the study were 200 age-matched blood donors, 100 male and 100 female, without any clinical history of diabetes and were considered healthy through routine laboratory analysis (Table 1).

The study was approved by the local Medical Ethics Committee and was conformant to the ethical guidelines of the Declaration of Helsinki. Venous blood samples were collected by venipuncture from all the subjects after 12 hours overnight fasting. Samples were analyzed on the day of collection for serum glucose and glycosylated hemoglobin. Levels of fasting glucose (GLU) and glycosylated hemoglobin (GHbA1c) were measured on the Olympus AU640 fully automated analyzer, using the commercial kits P.N. 1418-0013 and 1418-1057 by Medicon Hellas SA. Normal range established in Naval Hospital of Athens laboratory for GLU is 70 to 110 mg/dL and for GHbA1c is 4.4% to 6.2%. A strict quality control check by both internal and external controls was used for both tests.

Statistics

The statistical analysis was performed by SAS 9.3 for Windows (SAS Institute Inc. NC, USA) [24], as well as via Excel 2007 for Windows (Microsoft corporation) for data collection and preprocessing. In particular, we applied a linear regression model on four groups: male subjects with diabetes, female subjects with diabetes, male subjects without diabetes and female subjects without diabetes. Samples with outliers on scatter plot for data validity were excluded during data pre-processing. Differences between groups

were evaluated by the Student's *t*-test; the level of significance was set at $p = 0.05$ [25,26]. SAS 9.3 was used as well to calculate the power of the various statistical tests as well as the normality of the data.

Results

The statistical power of our sample when applying *t*-test, for sample size 352 for the female and 448 for the male patients was calculated for the mean GLU levels: 88% and for the mean GHbA1c 47%. Additionally the normality of the data was tested via the Shapiro-Wilk test, specifically for the female health controls it was $W=0.903$ ($p<0.0001$), for the male health controls $W=0.824$ ($p<0.0001$), while for the female patients: $W=0.793$ ($p<0.0001$) and for the male patients $W=0.793$ ($p<0.0001$). In this test for normality a value of *W* near to 1 indicates a perfect normal distribution and the related *p*-value the statistical significance.

The mean level of fasting blood glucose for male patients was 166.8 ± 49.3 mg/dL and the corresponding mean value for the GHbA1c was 7.05 ± 1.77 . Out of the 448 male patients, 201 had GHbA1c levels lower than 6.50%, while 134 had GHbA1c levels between 8.00 and 16.60%, reflecting their poor glycaemic control (Table 2).

The linear regression analysis suggests that there is a linear relation between GLU and GHbA1c. Moreover, the formula governing this relation is: $GLU=59.05+15.29*GHbA1c$ ($R^2=29.68\%$). The F-statistic of the overall model is highly significant ($F=188.20$ $p<0.0001$), as well as the slope and intersection parameters ($p<0.001$ both for slope and intersection) (Figure 1).

For the female patients the mean level of fasting blood glucose was 156.1 ± 46.7 mg/dL and the corresponding mean value for the GHbA1c was 6.81 ± 1.57 . Out of the 352 female patients, 192 had GHbA1c levels lower than $6.50 \pm 1.54\%$, while 54 had GHbA1c levels between 8.00 and 13.40%, reflecting their poor glycaemic control (Table 2). The linear regression analysis suggests that there is a linear relation between GLU and GHbA1c. Moreover, the formula governing this relation is: $GLU=40.74+16.95*GHbA1c$ ($R^2=32.41\%$).

Table 1: distribution of data according to disease status and gender.

	Type 2 DM		Total
	NO	YES	
FEMALE	100	352	452
MALE	100	448	548
Total	200	800	1000

Table 2: distribution of GHbA1c values in DM patients.

GHbA1c value %	MALE	FEMALE	GLYCAEMIC CONTROL
<5.00	16	15	excellent
5.00-5.49	24	38	very good
5.50-6.49	161	139	acceptable
6.50-7.99	49	106	suboptimal
8.00-9.99	64	35	poor
>10.00	134	19	very poor
TOTAL	448	352	

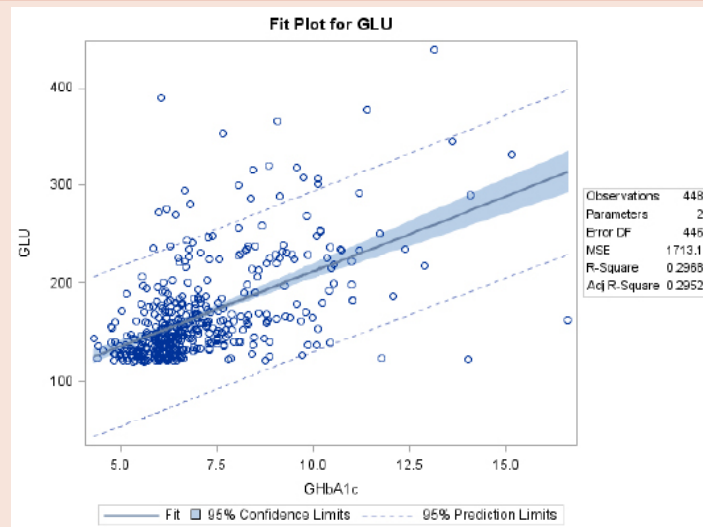


Figure 1: Linear relation between GLU and GHbA1c for male subjects with diabetes.

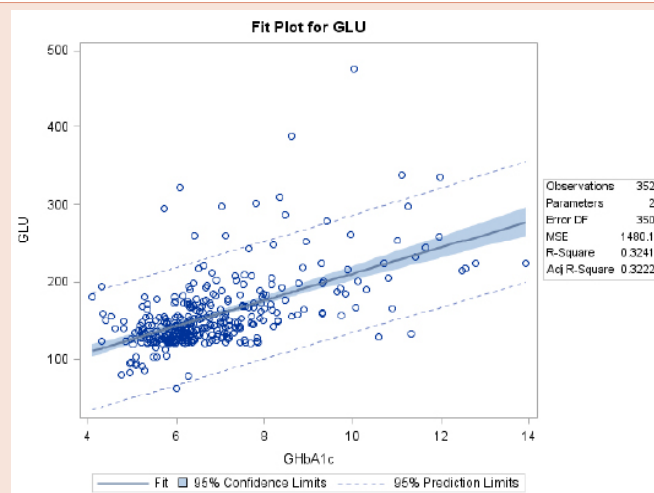


Figure 2: Linear relation between GLU and GHbA1c for female subjects with diabetes.

The F-statistic of the overall model is highly significant ($F=167.83$ $p<0.0001$), as well as the slope and intersection parameters ($p<0.001$ both for slope and intersection) (Figure 2).

Both equations (for male and female patients) have similar slope (15.29 and 16.95 respectively) meaning that equal increase in GHbA1c level reflects to similar increase in GLU level for both genders, however the intercept is different 59.05 for males and 40.74 for females, thus we expect that for male patients there is about 18.0 mg/dL higher GLU level than female patients for similar GHbA1c level.

Actually for male patients the mean GLU level is expected to be 10.7 mg/dL higher and this difference is statistically significant (pooled t-test: $t=-3.1$ $p=0.0019$), these findings are summarized in Table 3 and Figure 3.

Moreover, we evaluated a statistically significant difference in mean GHbA1c values between the two genders (pooled t-test: $t=-2.46$ $p=0.0142$). These findings are summarized in Table 4 and Figure 4.

In healthy controls, the mean level of GLU for male subjects was 92.5 ± 7.7 mg/dL and for female subjects 91.1 ± 6.8 mg/dL. The corresponding mean values for the GHbA1c were $5.28\pm 0.43\%$ and $5.26\pm 0.39\%$ respectively. The linear regression analysis showed that there is no correlation between GLU and GHbA1c ($R^2 = 0.0003$ and $R^2 = 0.0011$ respectively). These findings are presented in Figure 5.

Subsequently we estimated the average glucose (eAG) via the formula eAG (in mg/dL) = $28.7 \times A1C - 46.7$ using the measured GHbA1c values. There was statistically significant difference of the eAG mean values between the two genders (pooled t-test: $t= -2.00$ $p=0.0462$). These findings are presented in Table 5.

Table 3: Descriptive statistics for GLU in DM patients and healthy controls.

	SEX	N	Mean	Std Dev	Std Err	Minimum	Maximum
Patients	FEMALE	352	156.1	46.7	2.49	63.0	477.1
	MALE	448	166.8	49.3	2.33	120.1	438.5
Healthy controls	FEMALE	100	91.1230	6.8	0.68	69.1	99.9
	MALE	100	92.5470	7.7	0.77	64.3	100.0

Table 4: Descriptive statistics for GHbA1c DM patients and healthy controls.

	SEX	N	Mean	Std Dev	Std Err	Minimum	Maximum
Patients	FEMALE	352	6.81	1.57	0.08	4.10	13.93
	MALE	448	7.05	1.77	0.08	4.30	16.61
Healthy controls	FEMALE	100	5.26	0.39	0.04	4.33	6.87
	MALE	100	5.28	0.43	0.04	4.06	5.97

Table 5: Descriptive statistics for eAG in DM patients.

	SEX	N	Mean	Std Dev	Std Err	Minimum	Maximum
Patients	FEMALE	352	148.8	45.1	2.4	70.1	353.1
	MALE	448	155.6	50.4	2.4	76.7	430.0
Healthy controls	FEMALE	100	104.3	11.2	1.1	77.6	150.5
	MALE	100	104.7	12.2	1.2	69.8	124.0

Table 6: Correlation coefficients of GLU with eAG for the four groups according to gender and disease status.

	Females	Males
Healthy controls	N= 100, Cor. Coef. =0.03, p=0.74	N=100, Cor. Coef. =0.02, p=0.86
Patients	N= 352, Cor. Coef. =0.57, p<0.001	N= 448, Cor. Coef. =0.55, p<0.001

Comparisons between the eAG values (calculated via the aforementioned formula) and the measured GLU values. These comparisons were based on the Pearson correlation coefficient. First we compared GLU with GHbA1c and eAG irrelevant to gender and disease status. The scatter plots are presented in [Figure 7](#). From the analysis results we conclude that there is a statistically significant ($p < 0.0001$) strong correlation (Corr.Coeff.=0.64) between GLU and eAG. As it was expected the correlation between eAG and GHbA1c is perfect ($p < 0.0001$, Corr.Coeff =1.0) because GHbA1c and eAG were related via the aforementioned linear equation. There is a clear separation of the diabetics and non-diabetics as the scatter plots ([Figure 6](#)) present two distinct areas left lower part and upper right part.

From the comparison between GLU and eAG in relation to the disease status irrelevant to gender we conclude that their correlation for healthy controls is very low and not statistically significant (Corr. Coeff.=0.026, $p=0.71$) while their correlation for the DM patients is very good and statistically significant (Corr. Coeff.=0.56 $p < 0.0001$). The scatter plots for GLU with eAG irrelevant to gender for the two groups (healthy controls and diabetic subjects) are presented in [Figure 7](#).

From the comparison between GLU and eAG in relation gender and irrelevant to the disease status we conclude that there is no difference of the correlation between GLU and eAG between females

and males (Corr. Coeff. = 0.66 and 0.63 respectively) and that in both cases this correlation is statistically significant ($p < 0.001$). The scatter plots of GLU with eAG for the two genders with disease status indications are presented in [Figure 8](#).

As a final step, we examined the correlation between GLU and eAG in relation both to gender and disease status. For this analysis we calculated the correlation coefficient for the GLU with eAG for four groups: healthy female controls, female DM patients, healthy male controls, DM male patients. The correlation coefficients along with the statistical significance value and scatter plots for the four groups appear in [Table 6](#) and [Figure 9](#).

From this analysis we conclude that the correlation of GLU and eAG both for female and male healthy controls is neither statistically significant nor important (Corr. Coeff.=0.03 and 0.02 respectively, $p=0.74$ and 0.86 respectively). Thus gender is not important for this correlation of GLU and eAG of healthy controls. The correlation of GLU and eAG both for female and male DM patients is statistically significant and important (Corr. Coeff.=0.57 and 0.54 respectively, $p < 0.0001$ in both cases). As the two correlation coefficients do not differ statistically gender is not important for the correlation of GLU and eAG of diabetic patients, however as shown previously it was proved that GLU and eAG are correlated for the DM patients.

Study limitations

Within this study we studied various biochemical parameters related to D.M. and their relations. However it is not a population based study, moreover there was no random sampling, because we have used inclusion and exclusion criteria, hence generalization to large populations is not possible. Eventually, despite the rather small population, the results are valid due to their statistical p value.

Within this study we identified differences between the mean GLU levels of male and female patients; despite we have included subjects with DM duration more than a year, the disease duration, among other confounders, could be a factor that affects the results. These confounders could be a subject of a future study.

Another limitation is related to the short term fluctuations based of the measured levels of GLU and GHbA1c. Such fluctuations are dependent on the life style of the subjects as well as due to therapy; such fluctuations was not possible to be taken to account; as require 24x7 monitoring. However due to the large population and the concordance of the results with those of other studies, we suggest that the outcomes are representative.

As eAG is estimated via a linear relation from measured values of GHbA1c, the correlations of GLU with eAG are similar to these of GLU and GHbA1c.

Discussion

Diabetes mellitus is a chronic non communicable disease characterized by hyperglycaemia and associated with long-term complications. DM management requires an accurate evaluation of glycaemic control. The traditional blood glucose estimations give results that are influenced by biological variability, variability due to pre-analytical factors (such as blood collection method and blood

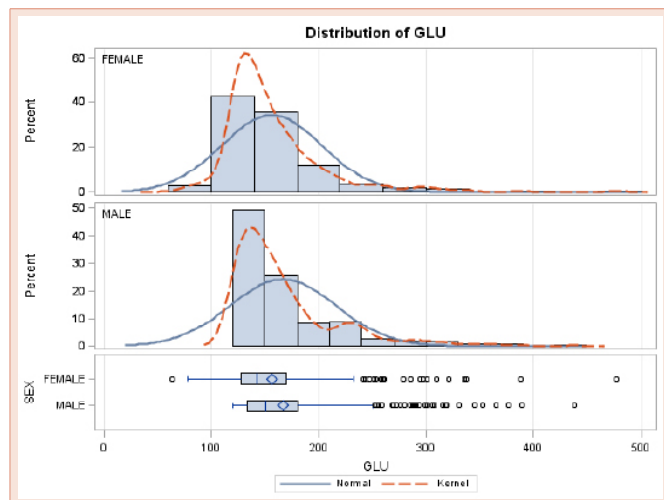


Figure 3: t-test for GLU levels in relation to gender.

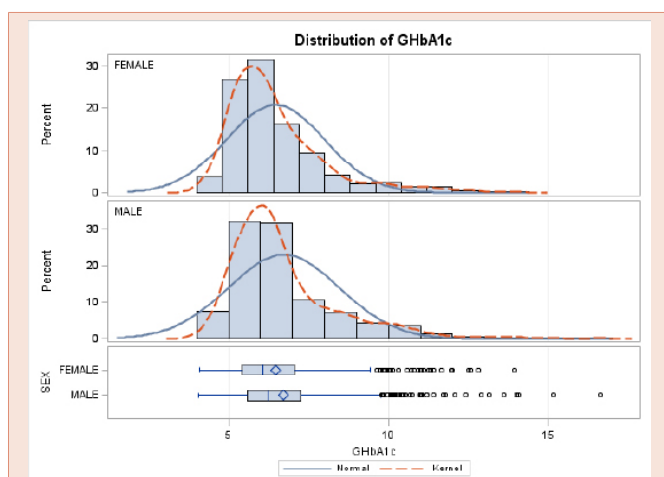


Figure 4: t-test for GHbA1c levels in relation to gender for DM patients.

storage conditions) and difficulty in ensuring fasting state before blood glucose measurement. GHbA1c measurements, expressed as a percentage of total blood hemoglobin concentration, have been widely used for more than 25 years [11,27]. GHbA1c measurements do not require a fasting state for sample collection, they present analytical variability of less than 2% and they provide information on glycaemic status over the past 2-3 months [11,21,27]. In the current study, GLU was correlated with GHbA1c in order to investigate the possible relationship between them in established diabetic patients in Greece. The possible influence of gender was also investigated. We found a linear relation between GLU and GHbA1c both in male and female patients. Moreover, the formulas governing this relation are: $GLU = 59.05 + 15.29 * GHbA1c$ and $40.74 + 16.95 * GHbA1c$ respectively. In both cases the relationship is highly significant. Male patients present higher GLU levels. Such differences have been also extensively reported by other authors and have been attributed to the impact of

sex hormones in glucose homeostasis as well as to different attitudes and behaviors related to diabetes care [28-30].

We have also evaluated a statistically significant difference in mean GHbA1c values between the two genders. Moreover, in our study 198 male patients (44.2%) and 54 female patients (15.3 %) presented poor glycaemic control with GHbA1c values greater than 8.00 %. The difference between the two genders with regard to poor glycaemic control was found statistically significant ($t = -2.46$ $p = 0.0142 < 0.05$). Poor glycaemic control over time has been linked to the development and progression of microvascular diabetes complications [6,11,21]. The literature is mixed on gender glycaemic control in type 2 diabetes. Some reports show gender equality in glycaemic control while others show differences between males and females [31-33]. Ethnic differences are also observed [34,35] and may reflect differences in the need and in the use of health services. In our study differences in GLU and GHbA1c levels between male and female healthy controls were not observed.

The correlation between GLU and GHbA1c for the total of population with DM under study was fairly high ($R = 0.557$, $p < 0.001$), while for the healthy population it was $R = 0.027$ ($p > 0.05$). Other studies have also reported similar correlations [36,37]. Conversely, a study conducted on the Dutch population showed only a moderate correlation, while a study in Southern India showed very high such correlation [38,39]. In our study since this correlation coefficient is around 0.55 and R^2 is about 0.3 (Figures 1,2) the eAG estimation alone by HbA1C, is unlikely to replace GLU measurements. The relationship between the fasting serum glucose level and the level of GHbA1c has been investigated in different studies, and many linear equations were developed for this purpose. In the present study we calculated the estimated average glucose (eAG) levels of our study group using Nathan's regression equation, which has been recommended by the American Diabetes Association: $eAG = (GHbA1c * 28.7) - 46.7$. Moreover, we investigated the relationship between the calculated eAG values and the measured GLU values. The eAG levels were positively correlated with the GLU levels in DM patients (Corr. Coeff. = 0.56) and this correlation is statistically significant ($p < 0.0001$). Since GHbA1c and eAG were related via a linear equation their correlation is perfect ($p < 0.0001$, Corr. Coeff. = 1.0). On the other hand their correlation for healthy controls is very low and not statistically significant (Corr. Coeff. = 0.026, $p = 0.70$). The possible influence of gender in this relationship was also investigated. From the comparison between GLU and eAG in relation gender and irrelevant to the disease status we conclude that there is no difference of the correlation between GLU and eAG between females and males (Corr. Coeff. = 0.66, and 0.63 respectively) and that in both cases this correlation is statistically significant ($p < 0.001$). Gender is not important for this correlation in healthy controls. Gender differences in eAG levels have also been observed by other authors [22,40]. For 279 samples (139 males and 140 females) the eAG levels were lower than the GLU levels, for 46 samples (22 males and 24 females) eAG and GLU levels were equal, whereas for 475 samples, (284 males and 191 females) the eAG levels were higher than the GLU levels. From these findings we conclude that the eAG and

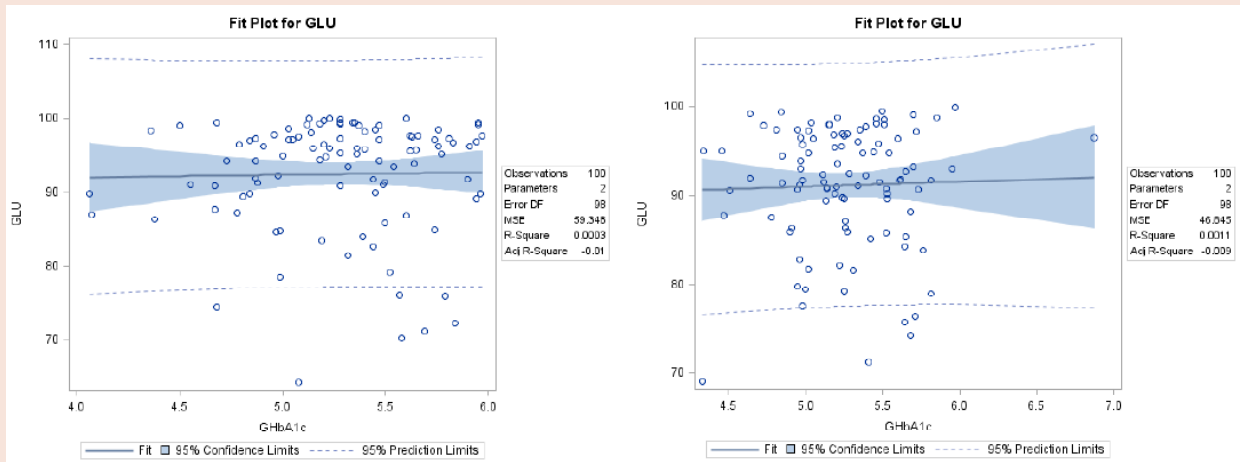


Figure 5: Relation between GLU and GHbA1c for male (left) and female (right) healthy controls.

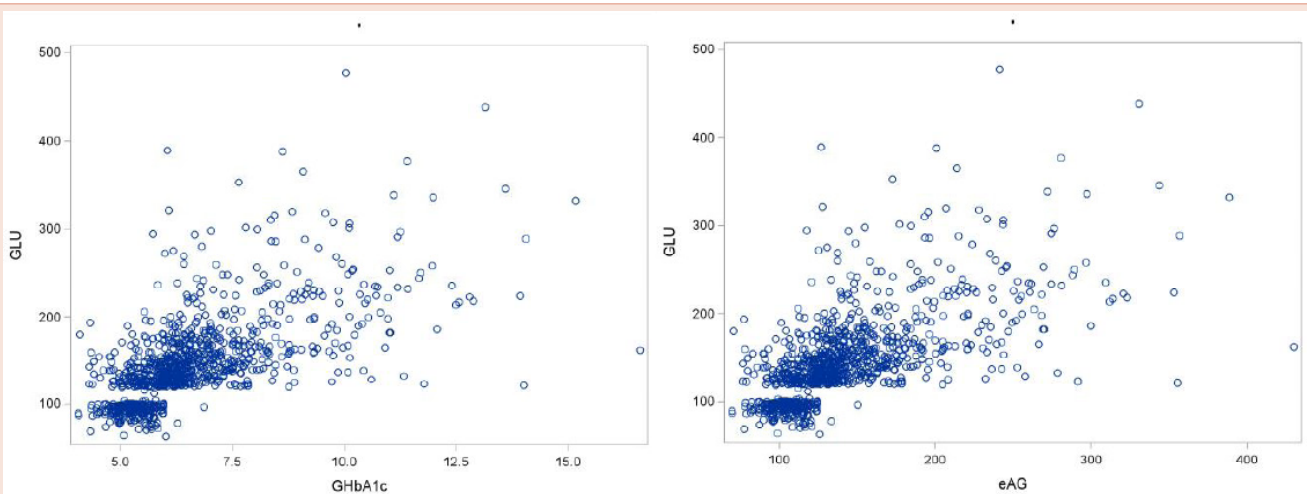


Figure 6: Scatter plots of GLU with GHbA1c (left) and GLU with eAG (right) irrelevant to the disease and the gender.

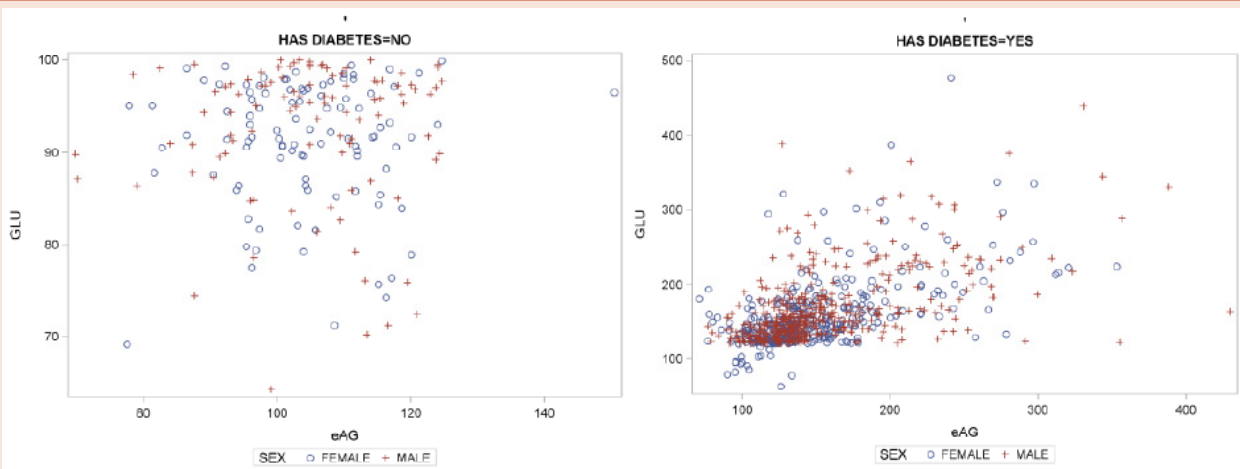


Figure 7: Scatter plots of correlations of GLU with eAG for healthy controls (left) and DM patients (right) gender is marked with different symbols.

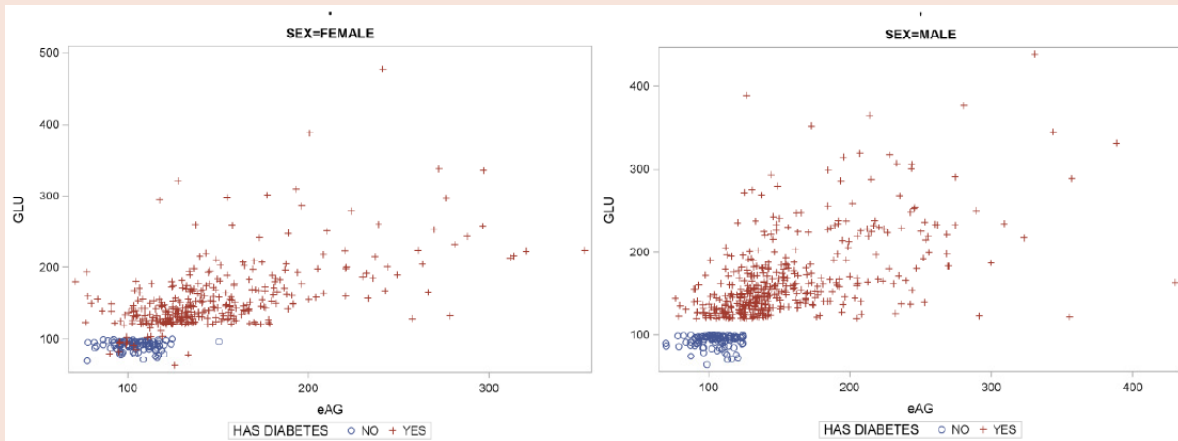


Figure 8: Scatter plots of correlations of GLU with eAG for females (left) and males (right) disease status is marked with different symbols.

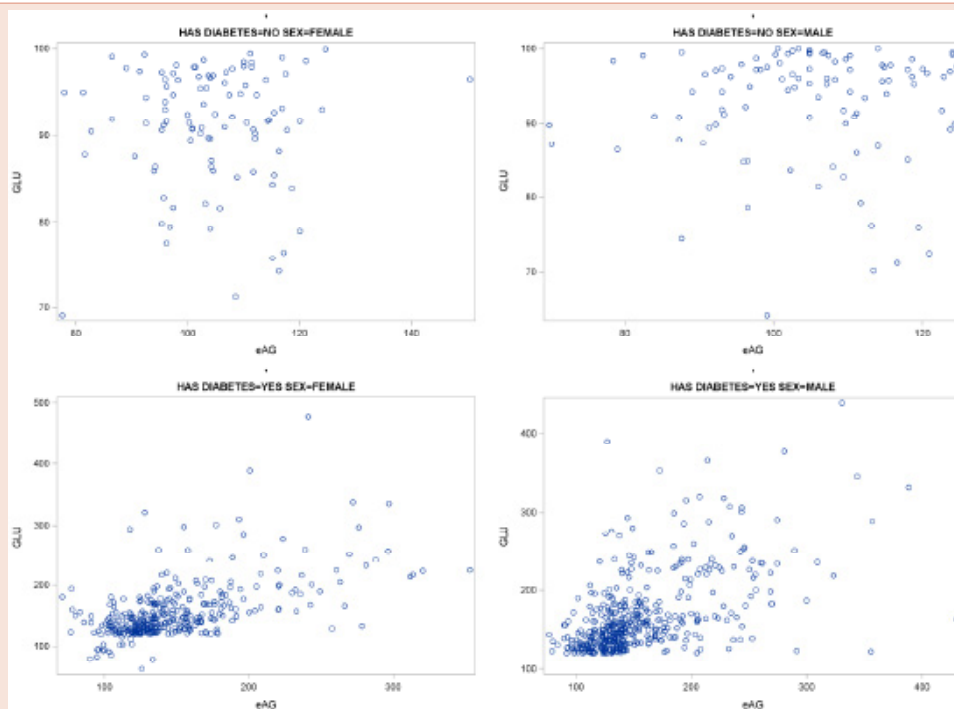


Figure 9: Scatter plots of correlations of the three variables for healthy female controls (a), healthy male controls (b), DM female patients (c) and DM male patients (d).

GLU values cannot be used interchangeably, because the eAG level is reflective of all plasma glucose levels over the previous two months [22,40-42]. Reporting eAG levels simplifies the interpretation of GHbA1c results. However, the idea of reporting an estimated result is not supported by the international clinical chemistry groups and the diabetes professional community, because calculations increase the uncertainty of test results. Moreover, the eAG calculation only provides an approximate estimation (90% of patient estimates fall within $\pm 15\%$ of the true average glucose) and additional studies of eAG in less-studied populations (ethnic minorities, pregnant females)

are needed in order to implement it worldwide, using a more holistic and integrated management [43]. Thus, one of the current strategies is the use of eAG levels together with GHbA1c values [44-46].

Conclusions

We found a linear relation between GLU and GHbA1c both in male and female patients. The formulas governing this relation are: $GLU = 59.05 + 15.29 * GHbA1c$ and $40.74 + 16.95 * GHbA1c$ respectively. In both cases the relationship is highly significant. Male patients present higher GLU levels. We also observed a statistically significant

difference in mean GHbA1c values between the two genders (198 male patients (44.2%) and 54 female patients (15.3 %) presented poor glycaemic control with GHbA1c values greater than 8.00 %). The difference between the two genders with regard to poor glycaemic control was found statistically significant. The correlation between GLU and GHbA1c for the total of population with DM under study was fairly high. The eAG calculation only provides an approximate estimation and additional studies of eAG in less-studied populations are needed in order to implement it worldwide. One of the current strategies is the use of eAG levels together with GHbA1c values.

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