Umm Al-Qura Univ. Medical J. Vol. 2, No.3, pp. 1-11 (2011)
01-06 © The University Press

UQU Medical Journal

Original Article

Glycaemic control markers fasting plasma glucose, glycated haemoglobin and fructosamine and their inter-relationship in non-diabetic and type 2 diabetes Saudi community

Abdullah A. Almarzouki
Departments of Internal Medicine, Umm Al-Qura University, Makkah, KSA.

Correspondence:
Dr. Abdullah A. Almarzouki
Assistant Professor Internal Medicine, Consultant
P.O. Box 13585
Faculty of Medicine, Umm Al-Qura University
Makkah
Mobile: 0504506292
e.mail: abuabid7@hotmail.com

Received: July 17, 2010 *Accepted: November 28, 2010*

استخدام المؤشرات البيوكيميائية للدالة على كفاءة تنظيم سكري الدم في مرض السكر (نوع 2)

عبدالله عبدالرحمن المرزوقي

استاذ مساعد , قسمم طب الباطنية

ص. ب. 13585- كلية الطب – جامعة أم القري – مكة المكرمة- المملكة العربية السعودية

الملخص العربي

الأهداف:استخدام قيم تركيز الهيموجلوبين المرتبط بالسكر و الفركتوزأمين والجلوكوزفي البلازما (حالة الصيام) كمؤشر للدلالة على كفاءة تنظيم سكر الدم في مرضى السكر (نوع 2) ودراسة الارتباط البيوكيميائي بين هذه المؤشرات الثلاث في مرضى السكر (نوع2) ومقارنتها بالأشخاص الأصحاء في المجتمع السعودي المكي.

الطريقة: عينة الدراسة تم إختيارهم عشوائياً من المجتمع المكي إناثاً وذكوراً أصحاء (359) ومرضى سكر (النوع 2) (246) تم تعيين الجلوكوز والفركتوزأمين والهيموجاوبين المرتبط بالسكر في عينات البلازما باستخدام COBAS plus 400 – INTEGRA والتحليل الإحصائي باستخدام WINKS SDA 2007 .

النتائج:لم نتمكن من إيجاد ارتباط بين جلوكوز البلازما (حالة الصيام) في اليوم الأول وقيم الفركتوزأمين أو الهيموجلوبين المرتبط بالسكر بعد 42 يوماً في مجموعة عينة الدراسة ((الأصحاء A)).

هنالك ارتفاع في تركيز الجلوكوز والفركتوزأمين والهيموجلوبين المرتبط بالسكر في البلازما في مرضى السكر نوع 2 عن الأصحاء . تركيز جلوكوز البلازما في حالة الصيام يتناسب طردياً مع مستوى الهيموجلوبين المرتبط بالسكر وكذلك الفركتوزأمين في مرضى السكر نوع 2 , هذه العلاقات لم يتم التوصل إليها في حالة الأصحاء. تشير النتائج إلى إمكانية استخدام هذه المؤشرات الثلاث في تشخيص ومتابعة مرضى السكر من نوع (2).

الخاتمة : قيم تركيز الجلوكوز والهيموجلوبين المرتبط بالسكر والفركتوز في الدم (حالة الصيام) لمرضى السكر (2) أعلى من قيم الأصحاء, وهنالك إرتباط بين هذه المؤشرات ويمكن استخدامها في تشخيص ومتابعة مرضى السكر (نوع 2)

ABSTRACT

Objective: To establish the reference ranges of fasting plasma glucose, HbA1c% and fructosamine, and the relationship among those glycaemic control markers in the non-diabetic and compared with type 2 diabetes Saudi population of Makkah city.

Materials and Methods: The study was conducted among 574 Saudi residents of Makkah, with 393 male and 181 female inhabitants. There was no history of diabetes in 328 individuals and the remaining 246 individuals were known to have type 2 diabetes mellitus. All participants were volunteers and randomly selected from the population of Makkah with aged ranged from 17 to 89 years. Type 2 diabetes subjects were selected according their previous diagnosis and clinical and biochemical finding. Pearson correlation is used to investigate the correlation among the glycaemic control markers.

Results: In type 2 diabetes fasting plasma glucose, HbA1c, and fructosamine levels were significantly higher 2, 2, and 1.5 fold than non-diabetic population. No correlation was observed among the estimated parameters in non-diabetic group whereas the in diabetic patients, the correlations were significant; r: 0.58, 0.66 and 0.71 for FPG vs. HbA1c, FPG vs. fructosamine, and HbA1c vs. fructosamine respectively, ($p \leq 0.001$).

***Keywords*:** Fasting plasma glucose, Fructosamine, Diabetes, Glycemic control, Glycated heamoglobin.

INTRODUCTION

Measurements of glycated haemoglobin (HbA1c) and fructosamine reflect the average of blood glucose concentrations over the preceding 6-12 weeks[1,2] and 2-3weeks[3,4] respectively. Both HbA1c and fructosamine determinations are used widely to assess the long-term[5,6,7] and short-term[8,9] glycaemia respectively, and to screen, diagnose and monitor glycaemic control in diabetes mellitus. The variations in HbA1c quantification and different reference ranges between different laboratories are attributed to diverse technical methods applied for the determination and the poor standardization[10] thus limiting the value as well as interpretation of the results.

Haemoglobinopathies, haemoglobin variants and hypertriglyceridaemia interfere with the estimation of HbA1c, where the value may be unreliable and inconsistent with a patient's clinical finding[11]. In such circumstances estimating fructosamine seems to be the method of choice for monitoring short-term glycaemia, [8,9,12,13] however with the limitation that <3.0 is not very low albumin concentration < 3.0 $g.l^{-1}$ may result in falsely low fructosamine value.

The aim of this study is to establish glycated haemoglobin and fructosamine along with fasting plasma glucose values as a measure of glycaemic control and to evaluate the relationship between these analyses in non-diabetic subjects and patients with type 2 diabetes in local Saudi community. This study was carried out in the absence of local and national reference ranges and lack of national standardization schemes for HbA1c and fructosamine determination. The use of locally derived values rather than national initiatives or international published values is beneficial and advisable since it is recommended that each laboratory should investigate the transferability of the expected values to their own patient's population and if necessary determine its own reference ranges.

A crucial element of modern below-knee amputation technique has been the more or less universal adoption of long posterior myoplastic flap,[10,11] as popularized by Burgess et al.[12] The healing of this flap is crucially dependent upon the blood supply. Considerable differences are noted in the various descriptions of how the posterior flap in below-knee amputation should be reconstructed.[10] One of these is whether to include or remove the soleus muscle that forms the main bulk of muscles in the posterior compartment of the leg at this level.[11]

The aim of the present work was to study the blood supply of the skin of the upper posterior aspect of the leg and the soleus muscle and to explore the anatomical basis of the possibility of excision of the soleus muscle from the posterior flap in below-knee amputations.

MATERIAL AND METHODS

Study population: This cross-sectional population study consisted of 605 volunteers categorized into three groups as under:

Group A: 31 healthy adults (17 male and 14 female, age ranged from 19-28 years) with no known history of diabetes mellitus. The group included in order to assess the relationship between HbA1c % or the concentration of fasting plasma fructosamine with single fasting plasma glucose value of the preceding 42 days.

We hypothesize that HbA1c and fructosamine values would not reflect the fasting blood glucose concentration of the same sample for the preceding 6 weeks.

Group B: 328 apparently healthy individuals (193 male and 135 female, between 17 to 89 years) with no previous history of diabetes mellitus.

Group C: 246 type 2 diabetes mellitus patients (200 male and 46 female, between 17 to 78 years) on oral hypoglycaemic medication.

Measurements of fasting plasma glucose, fructosamine and HbA1c were determined on the same sample in non-diabetic subjects (group B) and type 2 diabetes mellitus participants group C were expressed as mean ±SD. The values were used for reporting reference ranges for the studied population and for the assessment of the correlations among the glycaemic control parameters using regression analysis.

Setting: All participants were Saudi residents in Makkah, Saudi Arabia.

Laboratory assays

All biochemical analyses were determined at Medical Research Laboratory of Umm Al-Qura University using COBAS INTEGRA 400 plus, Roche. Blood was drawn by venipuncture from individuals fasted 8-12 hr, with Li-heparin as anticoagulant. Glucose concentration was determined in plasma by hexokinase method, the coefficient of variation (c.v.) within run 1.9 % and 1.4% at the means of 81.40 and 234.85 $mg.dl^{-1}$ and between run 2.1% and 1.7% at the means of 81.83 and 234.00 $mg.dl^{-1}$ respectively.

Haemoglobin A1c (HbA1c) was determined in whole blood by immunoturbidimetric method with final result expressed as a percent HbA1c (HbA1c%). The c.v. within run 1.3% and 2.1% at the means of 5.3 and 10.9 and between run are 1.6 % and 1.9% at the means of 5.3 and 11 respectively. Fructosamine was assayed colorimetrically in plasma free from haemolysis. The c.v. within run 2.4% and 2.8 % at concentrations 284 and 543 $\mu mol.l^{-1}$, and between run 2.3% and 3.1% at 282 and 537 $\mu mol.l^{-1}$ respectively.

Cholesterol was determined by enzymatic colorimetric method, HDL-cholesterol, LDL-cholesterol were measured with homogeneous enzymatic assay. Triglyceride was measured by enzymatic, colorimetric method. Urea and albumin were measured by kinetic test. Glutamate dehydrogenase, and colorimetric assay with endpoint method respectively.

Statistical analysis

All statistical analysis were performed using TexaSoft WINKS SDA software, Statistical data Analysis, 6.0.8, PROFESSIONAL, Edition 6, cedar hill, Texas, 2007. The statistical significance was evaluated by Student's t-test, and all p values were two-tailed test.
Linear regression, Pearson correlation analysis were used to assess the correlation among parameters.

RESULTS

Table1: shows the fasting plasma glucose (FPG), fructosamine concentrations, and HbA1c%, values for day zero and day 42 in group A. According to table, values for all measured parameters are within the reference range, for non-diabetic subjects. There is no statistical difference between the 1st and 2nd measurements of each parameter. The actual minimum and maximum values are 49-98 ($mg.dl^{-1}$), 4.5-5.9 (%), and 183-264 ($\mu mol.l^{-1}$) for glucose, HbA1c% and fructosamine respectively. Linear regression analysis shows no correlation between HbA1c% and the values of fasting plasma glucose of the preceding 42 day. The same finding for fructosamine, and no correlation was found between HbA1c and fructosamine values. The only correlations were reported in Table 1 between 1st and 2nd determinations of glucose, HbA1c and fructosamine.

Table 1: The relationship between HbA1c(%), fructosamine, and the fasting plasma glucose of the preceding 42 days in healthy subjects.

	Day zero estimate	Day 42 estimate	r ($p \leq 0.001$)
FPG ($mg.dl^{-1}$)	75.65 ± 9.49	73.94 ± 10.07	0.67
HbA1c (%)	5.00 ± 0.31	5.07 ± 0.27	0.84
Fructosamine ($\mu mol.l^{-1}$)	227.97 ± 17.22	228.00 ± 18.42	0.85

Table 1: Values are mean of 31 observations ± SD.
r : Pearson's correlation coefficient

Group B: Since no statistically significant differences were found for the estimated parameters between males and females in the non-diabetic (group B), and diabetic (group C), the data were all combined and presented as mean of each group in Table 2.
The confidence intervals about the mean 99% were 75.33-78.91 ($mg.dl^{-1}$), 5.05-5.23 (%), and 217-223 ($\mu mol.l^{-1}$) for fasting plasma glucose, HbA1c%, and fructosamine respectively for group B, and all means for the presented parameters in Table 2 for non-diabetic subjects fall within the reference values reported by the manufacturer. The usual practice of describing a reference range is as a mean **±2** SD**,** were for the studied non-diabetic population, as follow:
Fasting plasma glucose ($mg.dl^{-1}$) 52-102, HbA1c(%) 3.86-6.42, and fructosamine ($\mu mol.l^{-1}$) 178-262. The HbA1c% or fructosamine values do not correlate with fasting plasma glucose levels, also no significant correlation between HbA1c% and fructosamine values in non-diabetic population, the findings are consistent with those observed in group A.
Lipid profile (Total cholesterol, HDL-cholesterol, LDL- cholesterol, and triglycerides), urea, and albumin values are consistent with healthy individuals, in group B, whereas the values of the parameters in group C type 2 diabetes are statistically different from group B non-diabetic individuals, p-values are shown in the Table 2.

Table 2. Population characteristics and correlation among glycaemic control parameters in non-diabetic and type 2 diabetes

Values are the mean of the number of observations in parentheses ±SD.

	Non-diabetic (328)	Type 2 diabetes (246)	P-2 tailed
Age (years)	32.8 ±13.4	48.6 ±12.9	
range	17-89	17-78	
FPG ($mg.dl^{-1}$)	77.12 ±12.6	153.25 ±79	≤0.001
HbA1c (%)	5.14 ±0.64	9.85 ±3.7	≤0.001
Fructosamine ($\mu mol.l^{-1}$)	220 ±21	335 ±107	≤0.001
Total Cholesterol ($mg.dl^{-1}$)	171 ±32	179 ±42	≤0.008
HDL-Cholesterol ($mg.dl^{-1}$)	48 ±23	42 ±11	≤0.001
LDL- Cholesterol ($mg.dl^{-1}$)	106 ±28	114 ±34	≤0.004
Triglycerides ($mg.dl^{-1}$)	103 ±58	174 ±43	≤0.001
Urea ($mg.dl^{-1}$)	26 ±8	33 ±14	≤0.001
Albumin ($mg.dl^{-1}$)	4.3 ±0.5	4.2 ±0.4	≤0.005
r : pearson correlation			Combined values (574)
HbA1c vs FPG	0.07	0.58	0.73*
Fructosamine vs FPG	0.04	0.66	0.76*
HbA1c vs Fructosamine	0.17	0.71	0.81*

*** combined values (non-diabetic & type 2 diabetes population).**

Group C: As shown in the Table 2 the mean values of fasting plasma glucose, HbA1c% and fructosamine of the diabetic subjects are higher by 2.2 and 1.5 fold than the values of non-diabetic population respectively. The

$p \leq 0.001$. HbA1c values correlates well with FPG and fructosamine, and fructosamine correlates with FPG, $p \leq 0.001$. The r values for the correlation ships among the glycaemic parameters were shown in table 2, and the linear regression equations which illustrate these relationships in type 2 diabetes are:

$FPG\ (mg.dl^{-1}) = 32.7497 + (12.228\times\ HbA1c\%)$
$FPG\ (mg.dl^{-1}) = -8.6885 + (0.4837\times\ fructosamine\ (\mu mol.l^{-1}))$
$Fructosamine\ (\mu mol.l^{-1}) = 135.5614 + (20.2173\times\ HbA1c\%)$

DISCUSSION

Means and reference tested ranges of glycaemic control measures in healthy non-diabetic individuals (group A) are as follows:

The mean of FPG is about 77 $mg.dl^{-1}$, and the reference range is 52-102 $mg.dl^{-1}$. When the values of FPG were placed in to six categories, of 10 $mg.dl^{-1}$ intervals, and the corresponding mean values of HbA1c and fructosamine were tested using one-way analysis of variance, the average mean values across the categories of group A were not statistically different and indicate that all six categories are from a homogeneous population.

The mean of HbA1c is about 5.1 %, and the reference range is 3.9 - 6.4 %. When the values of HbA1c were placed in to 4 categories of 1% intervals and the corresponding mean values of FPG, and fructosamine were tested using one-way analysis of variance, the average mean values across the categories of the group were not statistically different, and indicate that all four categories are from a homogeneous population.

The mean of fructosamine is about 220 $\mu mol.l^{-1}$ and the reference range is 178 - 262 $\mu mol.l^{-1}$. When the values of fructosamine were placed in to 3 categories of 40 $\mu mol.l^{-1}$, intervals and the corresponding mean values of FPG and HbA1c were tested using one-way analysis of variance, the average mean values between the categories were not statistically different, and indicate that all categories are from a homogeneous population.

About 99% of the studied population (group B) fell within the reported reference ranges of FPG, HbA1c%, and fructosamine. Other estimated plasma chemistries (Total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, urea, and albumin) were within the normal ranges.

The relationships between the glycaemic parameters are as follows: In healthy subjects with no known history of diabetes mellitus although the fasting plasma glucose concentration was almost stable over a difference of 42 days(from day zero to day 42) with good correlation $r = 0.67$, $p \leq 0.001$, fasting plasma glucose do not represent the mean or average of blood glucose concentrations during the course of 42 days, a single fasting plasma glucose represents the glucose level at the time of sample withdrawal only, and reflects the physiological glycaemic control. The statistically significance ($p \leq 0.001$) correlation between matched values of glucose, HbA1c and fructosamine indicate the stability of these parameters (glycaemic control) during the course of the investigation. The absence of correlation between the values of HbA1c% or fructosamine with the preceding 42 days values of fasting plasma glucose does not contradict that HbA1c and fructosamine levels, reflecting the average of plasma of glucose the preceding 6-12 and 2-3 weeks.[1,2,3,4] FGP level which represents just one point (lowest) of about seven points measurements were used to estimate the mean of plasma glucose[14]. The higher value of Pearson's correlation coefficient for HbA1c% and fructosamine in comparison to glucose may indicate the stability of these parameters and less variation than FPG estimate, hence more reliable indicators for measuring past short- and long-term glycaemic control during the course of treating diabetes mellitus or even looking for the past (2-12) weeks glycaemic control in healthy subjects.

No correlation was found among the estimated glycaemic parameters in non-diabetic population (group B), and in group A. FPG does not represent the prevailing mean plasma glucose concentration, whereas in diabetic subjects (group C), FPG well correlated with

HbA1c and fructosamine measurements, and HbA1c well correlated with fructosamine. The loss of the correlation in non-diabetic population could be due to narrow physiological ranges of FPG, HbA1c and fructosamine, since all data points clustered around the mean of the population, and fall at the bottom of the regression line, so incomplete and invalid data sets limit to derive the correlation. This represents the stable physiological state rather than the pathological state of diabetes, whereas strong correlation among the broad distribution ranges of glycaemic parameters. Moreover combined data of non-diabetic and diabetic population showed a stronger correlation, and the predicted values are lower than those predicted by using diabetic population data.

The correlation of fructosamine with FPG and HbA1c in diabetic and combined (diabetic and non-diabetic) population were reported.[15,16] A poor, moderate and strong correlation between FPG and HbA1c in non-diabetic, diabetic + non- diabetic and diabetic population, were observed respectively.[17] Our results however support stronger correlation in combined data population. Also a strong correlation between HbA1c and preprandial glucose in type 2 diabetes, was observed.[18]

From linear regression analysis, we report that for each 1% in HbA1c represents about 12mg.dl^{-1} FPG or 20 µmol.l^{-1} fructosamine, and 20µmol.l^{-1} fructosamine increase corresponds to about 10 µmol.l^{-1} FPG in type 2 diabetes population.

The correlation between HbA1c and mean plasma glucose is reported in longitudinal and cross-sectional studies in type 1 and 2 diabetes as well as general population, and showed variable predicted estimates of mean plasma glucose, 1% rise in HbA1c represents 18 to 36 mg.dl^{-1} rise in average plasma glucose.[14,19,20,21,22] The glycation of haemoglobin is influenced by erythrocyte life-span, haemolobinopathies, glucose transmembrane gradient, age, and race,[24,24,25] under such condition FPG and fructosamine are valid as glycaemic control markers.

In diabetic subjects FPG, HbA1c, and fructosamine values are significantly higher than non-diabetic, this indicates the persistent of hyperglycaemia in diabetic population, and estimating mean plasma glucose is impractical for patients and physician, so FPG along with HbA1c and fructosamine are valid parameters to monitor glycaemic control and provide important feedback to physician and patient. Discordance among these parameters suggests revising patient's blood disorder, diet and exercise behavior, or even medication regimen.

Although the size of studied population is comparable with other published work, it could limit the study. The volunteers past health history, clinical picture, and plasma chemistries are normal, but not performing OGTT to exclude undiagnosed diabetes could have limitation.

CONCLUSIONS

Fasting plasma glucose, HbA1c, and fructosamine values are significantly higher in type 2 diabetes than non-diabetic population. Linear regression analysis demonstrated that FPG, HbA1c, and fructosamine are valid markers for glycaemic control in type 2 diabetes and non-diabetic population.

ACNOWLEGMENT

I thank Miss Samerah Omar Nazalawe for secretarial skill and Mr. Ibn Idrees Mustafa for his technical assistance.

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