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Role of glycated albumin and glycated hemoglobin in prediction of coronary artery disease using regression model in South Indian population

Elancheran Malligai ,[1]Sreyankumar Malini [2], Pradeep G Nayar [3]

The Chettinad Hospital & Research Institute, Rajiv Gandhi Salai, Kelambakkam, Kancheepuram District, Tamil Nadu. 603103.
1- Professor & HOD, Department of Biochemistry. 2- PG, Department of Biochemistry. 3- Professor, Dept of Cardiology.

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Corresponding Author:

Dr. Malligai.E, Professor and Head, Department of Biochemistry, The Chettinad Hospital & Research Institute, Rajiv Gandhi Salai, Kelambakkam, Kancheepuram District, Tamil Nadu 603103. Email: malli.murugesan@gmail.com

Abstract:

Background: Glycated proteins through the formation of Advanced Glycation Endproducts (AGE), have a role in the development of atherosclerosis. Keeping this background in mind, we have designed a study as prediction of coronary artery disease using clinical value of Glycated Albumin and Glycated Hemoglobin. **Materials and Methods:** Subjects (n= 79) were categorized into CAD positive (n=63) and CAD negative group (n=16) by angiographically proven stenosis. After obtaining informed consent, clinical History, Baseline Parameters were recorded. Serum levels of Glycated albumin and Glycated hemoglobin as well as other variables were determined. Predictors of CAD were analyzed using logistic regression model and Receiver Operating Characteristic (ROC) curve. **Results:** Unpaired "t" test showed significant increase in Glycated albumin and Glycated hemoglobin values in CAD positive group. Logistic regression analysis was used to find out the sensitivity & specificity, odds ratio of Glycated hemoglobin and Glycated albumin. The model for predicting CAD was P/ (1-P) = EXP (-6.97+ 0.12 AGE + 1.08 GENDER + 0.113 BMI + 1.09 DIABETES + 0.50 HYPERTENSION + 0.978 SMOKING + 0.008 ALCOHOLIC + 0.009 GLYCATED ALBUMIN + 0.137 HbA1c). In ROC curve, Area under the Curve (AUC) of Glycated albumin is 0.791(95% CI 0.678 – 0.904, p<0.001) and for Glycated hemoglobin 0.713(95% CI 0.569 – 0.856, p <0.05). The regression model showed AUC of 0.80(95% CI 0.694 -0.918 p value <0.001). **Conclusion:** The mean of both groups showed highly significant difference, regression analysis and ROC curve showed the Glycated albumin is highly significant than Glycated haemoglobin.

Key words: CAD; Diabetes; Glycated Albumin; Glycated Hemoglobin; South India.

Introduction

Coronary Artery Disease, a non-communicable disease is the leading cause of death worldwide currently. It tops the list released by World Health Organization (WHO) and kills around 7 million per year [1]. Experts have predicted that the percentage can raise upto 40 around 2020. Though the occurrence is sudden in most of the individuals, the disease progresses silently without any signs and symptoms for decades [2]. Considering this, it is mandatory to dig out all the tools to screen susceptible patients. The results of large studies have shown that Hyperglycemia and Glycated Proteins are independent risk factors for vascular complications [3,4]. In rapidly developing countries like India, the percentage of feedlot syndrome is quite high due to life style changes and stress. Hence, this study was undertaken with the hypothesis that Glycated Proteins lead to formation of Advanced Glycation End Products (AGE), one of the factors involved in the development of atherosclerosis and to find out the efficacy of clinical values of Glycated Hemoglobin and Glycated Albumin in the prediction of CAD in south Indian population [5].

Materials and Methods

It is an analytical retrospective case control study done with seventy-nine subjects who were admitted in Cath ICU, Chettinad Hospital and Research Institute, Kelambakkam, Chennai over a period of 6 months from Dec 2012 to May 2013. After obtaining approval from the Institutional Ethical committee, subjects who underwent Coronary Angiogram at Cath ICU were chosen irrespective of other chronic ailments they had. Subjects were alienated into CAD positive and CAD negative groups based on their angiogram report. Informed consent was obtained from subjects before enrolling them in the study. Personal data about the subject was obtained as questionnaire. Height and weight were measured with calibrated scale and BMI was calculated using formula weight in kilogram divided by height in meter square.

5ml of venous blood was drawn from all subjects in EDTA(lavender) tube for Glycated Hemoglobin and Plain (red) tube for the estimation of Glycated Albumin, blood Urea Nitrogen and Creatinine. All the samples were processed immediately. *D10 BIORAD* analyzer was used to estimate Glycated Hemoglobin with principle of Ion exchange High Performance Liquid chromatography. Its linear range was 3.8% to 18.5% and interassay coefficient was 1.6%. Glycated Albumin was measured using NitroBlue Tetrazolium Method using *Spinreact, Spain kit* in *Merck 300* Semi auto analyzer with interassay Coefficient of variation of 2.12%. BUN and creatinine was analyzed by Urease and Jaffe Kinetic method in Dade Behring Xpand with CV of 2.9 %

Coronary angiography was done through femoral route using standard Modified Judkin's Method by Interventional cardiologist who was blind about the study protocol

Statistics:

All statistical analyses were performed using SPSS for Windows 21.0 (IBM SPSS Statistics 21.0). Differences between groups were assessed using unpaired 't' tests. Multivariate analysis was performed using logistic regression to determine each variable's predictive ability. The predictive values of Glycated albumin and Glycated hemoglobin in the logistic regression model were calculated by constructing Receiver-Operating Characteristic (ROC) curve. A 'p' value of <0.05 was considered statistically significant.

Results

Baseline Clinical Characteristics: We have presented the data as frequencies and percentages for categorical variables (Gender, diabetes, alcohol, and smoking) and mean ± SD for continuous variables (Age, Glycated Hemoglobin and Glycated albumin) unless otherwise indicated. (Table -1). Significance levels were calculated by unpaired 't' test.

Logistic regression model

Serum glycated albumin and Glycated hemoglobin levels were significantly increased in CAD than in controls (Table 1). The logistic regression model for predicting CAD was defined as: P/ (1-P) = EXP (-6.97+ 0.12 AGE + 1.08 GENDER + 0.113 BMI + 1.09 DIABETES + 0.50 HYPERTENSION + 0.978 SMOKING + 0.008 ALCOHOLIC + 0.009 GLYCATED ALBUMIN + 0.137 HbA1c) and the probability value for each patient was then calculated by equation: $P = e^y/1+e^y$, where y = ln [P/(1-P)]. Hosmer-Lemeshow test was used to check the models' goodness of fit and the results demonstrated a good fit achieved (goodness of fit: Hosmer-Lemeshow $\chi 2 = 6.763$, d.f. = 8, P = 0.562). The sensitivity and specificity of Glycated albumin through logistic regression was 92% and 18% respectively. Similarly, for Glycated Hemoglobin sensitivity was 94% and specificity 12%.

Table 1: Significance of Baseline Characters and Biochemical Parameters

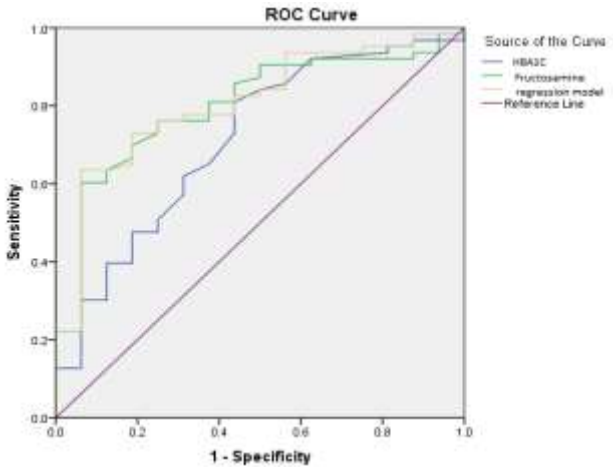
S.NO	VARIABLE	CONTROL(n=16)	CASES (n=63)	p-VALUE
1	AGE(yrs)	51.8±7.6	54.8±9.2	NS
2	MALE (%)	11(68.75)	46(73.0)	NS
3	BMI	26.29±5.00	27.53±3.9	NS
4	DIABETES (%)	5(31.25)	37(58.7)	0.049975
5	HYPERTENSION (%)	5.0(31.25)	31(49.2)	NS
6	SYSTOLIC BP (mm Hg)	135.75±21.3	135.98±23.8	NS
7	DIASTOLIC BP (mm Hg)	87.3±11.04	86.14±12.74	NS
8	SMOKING (%)	2(12.5)	19(30.1)	NS
9	ALCOHOL (%)	2(12.5)	15(23.80)	NS
10	BUN (mg/dl)	11±4.28	10.55±3.33	NS
11	CREATININE (mg/dl)	0.92±0.28	0.94±0.24	NS
12	GLYCATED ALBUMIN(µmol/L)	254.15±101.07	376.50±112.25	0.000424
13	HbA1c (%)	5.29±1.40	6.54±1.9	0.020691

p-value <0.05 is significant; NS- Not Significant, BUN-Blood Urea Nitrogen; BMI- Body Mass Index. Continuous Variables were expressed in Mean ± Standard Deviation; Discrete variables were expressed in number count with percentage in parenthesis.

Receiver-operating characteristic curves

The probability value of glycated albumin to predict CAD was 0.791 and glycated hemoglobin is 0.713. The probability value of regression model curve incorporating both HbA1c and Glycated Albumin was having Area of 0.806 *Table (2).* The interpretation of ROC curve is as follows 0.97-1.0 = excellent, 0.92-0.97 = very good, 0.75-0.92 = good, 0.50-0.75 = fair. (*Figure 1*)

Figure 1: ROC curve for glycated albumin, Glycated Hemoglobin and logistic regression model for predicting coronary artery disease



The *AUC of Glycated Albumin and Glycated Hemoglobin are 0.791 & 0.713 respectively.*

Table 2: Diagnostic performance of Glycated albumin, Glycated Hemoglobin and logistic regression model

VARIABLE	AREA UNDER THE CURVE(AUC)	95% CI
Glycated Albumin	0.791	0.678-0.904
Glycated Hemoglobin	0.713	0.569-0.856
Regression model	0.806	0.694-0.918

Discussion

Coronary artery disease (CAD), is a major cause of morbidity and mortality especially in type 2 diabetes mellitus (T2DM) [6,7]. Various factors are contributing to the risk of cardiovascular diseases, which include hyperglycemia, fluctuation of blood glucose, central obesity, hyperlipidemia and hypertension and so on. Glycemic disorders are important components of these risk factors.

Interventional studies have established that cardiovascular complications were mainly or partly dependent on sustained chronic hyperglycemia [8]. Glycemic status can be estimated as a whole from determination of hemoglobin A1c (HbA1c) level, which integrates hyperglycemia of 8 weeks. However, CAD risk were not solely limited to sustained chronic hyperglycemia but can be extended to the glycemic variability with acute glucose changes which has more deleterious effect than sustained hyperglycemia [9,10]. Glycated Albumin, a predominant Glycated protein gives idea about blood glucose levels of last 2 weeks and adds more information on atherosclerosis alone or in combination with HbA1c.

In our study, the subjects mean age was 54 with pre obese BMI and male gender as significant contributors. Logistic Regression model showed both Glycated Albumin and Glycated Hemoglobin has moderate potency to screen CAD (area under curve: 0.791, 0.713 respectively). Both were Glycated proteins, and produce Advanced Glycated End Products (AGE), a proinflammatory marker [11,12]. AGE led to endothelial injury and inflammation by inducing IL8, E Selectin from endothelial cells and IL6, monocyte chemotactic peptide from vascular smooth muscle cells and generates Reactive Oxygen Species through Protein Kinase C pathway [13-16]. Out of 63 subjects in CAD positive group, 21 subjects (33%) had elevated HbA1c but 51 subjects (82%) showed elevated Glycated Albumin. Glycated Albumin was a significant predictor than Glycated Hemoglobin in CAD probably due to Short turnover time (20 days) and its ability to reflect acute changes in glucose concentration quickly than glycated hemoglobin.

This was consistent with study done in Japan, which quoted that Glycated Albumin was better marker than HbA1c in hemodialysis patients [17]. Another study done by Pu. LJ, Lu. L, with 320 subjects with diabetes showed Glycated Albumin is a significant predictor than HbA1c [18]

Even though we proved a moderate potency of the two glycated proteins in the prediction of Coronary artery Disease with > 90% sensitivity in South Indian population, we were unable to derive a proper specificity which was probably due to small sample size collected over a period of 6 months and inability to derive a cut off point for prediction of CAD from this population Size.

Conclusion

The results were consistent with our hypothesis that Glycated proteins had a definitive role in prediction of CAD. However, studies with large sample size are required to confirm the results.

Source of Funding: Nil

Conflicts of Interest: Nil

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