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Original Research Article

Hemoglobin Glycation Index and Renal Function Decline in Type 2 Diabetes Mellitus

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Abstract:

Background: Hemoglobin glycation index (HGI) was introduced to overcome the individual variations in the measured HbA1c (M-HbA1c) levels. Increased HGI levels were associated with risk of diabetic complications and morbidity. So, we aimed to evaluate the predictive utility of HGI towards systemic risk markers for cardiovascular and renal diseases in type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study included diabetic cases (n = 100) and non-diabetic controls (n = 50). Biochemical parameters of diabetic profile including M-HbA1c, renal profile, and cardiovascular risk markers including lipid profile were estimated using standardized assay methods and compared between the study groups. Their standardized HGI were calculated using linear regression based predicted HbA1c (P-HbA1c) levels. Correlations of HGI and M-HbA1c with the risk markers of systemic diabetic complications such as renal and lipid profile were analysed.

Results: Greater variations between M-HbA1c and P-HbA1c levels, resulting in higher HGI levels were observed in the diabetic group than controls. Among the systemic risk markers, serum creatinine and triglyceride had significant elevations in diabetic group ($p < 0.05^*$). Compared to M-HbA1c, HGI levels had stronger correlations with increasing serum urea ($r = 0.3164$, $p = 0.0013^*$), serum creatinine ($r = 0.4073$, $p = 0.00003^*$) and declining eGFR levels ($r = -0.3512$, $p = 0.0003^*$) in diabetics. No such significant correlations were observed between HGI and lipid profile cardiovascular risk markers.

Conclusion: Higher HGI levels in diabetes suggest the possible role of HGI in monitoring glycemic control. The significant correlations of higher HGI levels with declining renal function emphasise the predictive utility of HGI for early detection of renal diseases in T2DM.

Keywords: Diabetes mellitus, Glycated hemoglobin, Hemoglobin glycation index, renal disease.

Introduction

Diabetes mellitus (DM) is a prevalent non-communicable disease globally and in India. Poor glycemic control is associated with several systemic complications of diabetes. Glycated hemoglobin (HbA1c), being a gold standard measurement of glycemic control, is used to routinely diagnose and monitor diabetic patients [1]. Several studies demonstrated the associations of increased HbA1c levels with the risk for diabetic complications, thus suggesting the use to HbA1c as predictor of adverse diabetes outcomes [2,3].

Early risk identification and treatment are important to prevent diabetes related morbidity and mortality. This has also led to stringent glycemic control strategies in order to prevent the incidence of diabetic complications in subjects with higher HbA1c. But on the contrary, such management plans aimed at lowering HbA1c levels were found to have harmful effects on the diabetes patients studied due to the danger of hypoglycaemia [4]. Moreover, despite the availability of standardized measurement assays, greater inter-individual variations were observed in HbA1c levels within the same glycemic levels. This may be due to the biological factors affecting glucose metabolism and hemoglobin glycation process [5].

These findings questioned the predictive utility of HbA1c on diabetic complications and associated morbidity. So the hemoglobin glycation index (HGI) was introduced as an alternative measure as it remains unaffected by the biological variations affecting HbA1c. HGI is the difference between

measured (M-HbA1c) and predicted (P-HbA1c) HbA1c levels, where the latter is determined by standardized linear regression of fasting plasma glucose (FPG) and HbA1c levels [5,6].

Several trials have demonstrated the associations of higher HGI levels with increased diabetic morbidity and mortality due to adverse cardiovascular events, other microvascular and macro-vascular complications [7,8]. However few studies failed to reproduce similar predictive associations of HGI [9]. So here we aimed to evaluate the predictive correlations of standardized HGI with systemic risk markers for cardiovascular and renal diseases in our diabetic study population.

Materials and Methods:

This cross sectional study was conducted in the patients visiting medical outpatient department (OPD) of a tertiary care hospital in South India. The study was approved by the institutional ethical committee. The study participants were included after obtaining informed consent.

The study included 150 adult participants above 18 years of age, of whom only those with a prior clinical diagnosis of type 2 diabetes mellitus (T2DM) were considered as diabetic cases (n = 100), while the remaining participants were grouped as controls (n = 50). Subjects with a history of pre-existing cardiovascular diseases, renal diseases, diabetic complications, hemoglobinopathies, anemia, incomplete clinical records were excluded from the study.

Relevant medical history, anthropometric parameters like height, body weight, body mass index (BMI) and waist circumference (WC), clinical data, laboratory investigation reports were collected from all the participants.

Laboratory data of the subjects included the following blood investigation reports such as FPG, post-prandial or 2-hour plasma glucose (2h-PG) during a 75g oral glucose tolerance test (OGTT), HbA1c, serum urea, serum creatinine, eGFR (calculated from serum creatinine using CKD-EPI creatinine equation), spot urine protein-creatinine ratio (urine PCR), fasting serum lipid profile including total cholesterol (TC), triglycerides (TGL), HDL-cholesterol (HDLc), LDL-cholesterol (LDLc). All laboratory measurements were performed using standardized methods using Roche Cobas c311 auto-analyser. Standardized linear regression equations of P-HbA1c = (0.024 x FPG) + 3.1 were used to calculate HGI = (M-HbA1c) - (P-HbA1c), as given by the U.S. National Health and Nutrition Examination Survey (NHANES) on multiethnic study population [6].

Statistical analysis:

The study data of all participants were compiled in spreadsheets. Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), while the categorical variables were expressed as frequencies and percentages. Unpaired t-test and Mann Whitney U-test were used to compare the continuous variables between cases and control groups.

The categorial data were compared between the study groups using Chi-square test. Correlations of M-HbA1c and HGI with other study variables were determined using Pearson and Spearman's correlation analyses. The data were analysed using statistical software SPSS 20.0 and p-value < 0.05 was considered as statistically significant.

Results:

The study participants (n = 150) were all above 30 years of age, with a mean age of 53.19 $\pm$ 10.22 years. On the whole, there were 60 females (40%) and 90 males (60%). The participants were divided into control group (n = 50) and diabetic cases (n = 100), based on the clinical diagnosis. The subjects in the study groups were of similar age group. The diabetic group had more males than females. The diabetic subjects also had higher mean BMI levels than the non-diabetic controls.

The diabetic profile including FPG, 2h-PG, M-HbA1c, P-HbA1c were significantly higher in the diabetic group, except for the standardized HGI (Table 1).

Table 1: Demographic characteristics and diabetic profile of the study groups

Parameter	Control group (n = 50)	Diabetic group (n = 100)	Table value	p value
Age (years)	53.76 $\pm$ 11.64	52.91 $\pm$ 9.48	0.4789	0.6327[a]
Females (%)	26 (52%)	34 (34%)	4.5	0.0339[c*]
BMI (Kg/m^2)	24.28 $\pm$ 6.23	26.26 $\pm$ 4.52	2.21	0.0283[a*]
WC (cm)	93.85 $\pm$ 11.87	96.23 $\pm$ 10.57	1.2448	0.2152[a]
Systolic Blood Pressure (mm Hg)	125.6 $\pm$ 20.02	127.7 $\pm$ 19.89	0.6083	0.5439[a]
Diastolic Blood Pressure (mm Hg)	81.04 $\pm$ 12.33	81.26 $\pm$ 10.95	0.1112	0.9117[a]

FPG (mg/dL)	97.5 (84, 116)	186.5 (140.75, 236.25)	8.4738	< 0.00001[b*]
2h-PG (mg/dL)	147 (128.25, 169)	288.5 (214, 361)	9.0120	< 0.00001[b*]
M-HbA1c (%)	5.60 ± 0.74	8.20 ± 1.08	15.3169	< 0.00001[a*]
P-HbA1c (%)	5.48 ± 0.45	7.85 ± 1.84	8.9565	< 0.00001[a*]
HGI	0.12 ± 0.67	0.35 ± 1.66	0.9297	0.3540[a]
a - Independent t test, b - Mann Whitney U test, c - Chi square test, * - Significant p value < 0.05				

In the correlation analyses, M-HbA1c only had weaker correlation with the serum urea levels in diabetic subjects. But HGI had much more stronger positive correlations with the renal function tests of serum urea and serum creatinine levels, and a significant negative correlation with the eGFR levels in the diabetic subjects. No significant correlations were observed between the M-HbA1c or HGI and the lipid profile parameters which serve as the cardiovascular risk markers (Table 3, Figures 1 and 2).

Table 2: Other biochemical parameters of the study groups

Parameter	Control group (n = 50)	Diabetic group (n = 100)	Table value	p value
Serum urea (mg/dL)	22 (18.25, 29)	23 (19, 30.25)	0.6718	0.5029[b]
Serum creatinine (mg/dL)	1 (0.9, 1.1975)	1.1 (0.92, 1.4)	2.0691	0.0385[b*]
eGFR (mL/min)	74.94 ± 21.97	67.43 ± 23.71	1.8724	0.0631[a]
Spot urine PCR	0.125 (0.09, 0.19)	0.155 (0.09, 0.505)	2.0512	0.0404[b*]
Serum TGL (mg/dL)	127.5 (78.5, 160.5)	145.5 (105.75, 191.25)	2.0791	0.0375[b*]
Serum TC (mg/dL)	162.72 ± 51.48	176.68 ± 49.42	1.6084	0.1099[a]
Serum HDLc (mg/dL)	39.2 ± 9.83	38.32 ± 9.11	0.5430	0.5879[a]
Serum LDLc (mg/dL)	97.06 ± 34.64	106.49 ± 32.17	1.6493	0.1012[a]
a - Independent t test, b - Mann Whitney U test, * - Significant p value < 0.05				

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Table 3: Correlation analyses of HbA1c and HGI with biochemical parameters of the diabetic group

Parameter	M-HbA1c (%)		HGI	
	Correlation coefficient	p value	Correlation coefficient (r)	p value
Serum urea (mg/dL)	0.2247	0.0246[b*]	0.3164	0.0013[b*]
Serum creatinine (mg/dL)	0.1011	0.3169[b]	0.4073	0.00003[b*]
eGFR (mL/min)	-0.1797	0.0748[a]	-0.3512	0.0003[a*]
Spot urine PCR	0.1154	0.2529[b]	0.1524	0.1301[b]
Serum TGL (mg/dL)	0.0196	0.8466[b]	-0.0314	0.7561[b]
Serum TC (mg/dL)	0.0453	0.6545[a]	-0.092	0.3626[a]
Serum HDLc (mg/dL)	0.0434	0.6681[a]	-0.0905	0.3732[a]
Serum LDLc (mg/dL)	0.0265	0.7935[a]	-0.0899	0.3786[a]
a - Pearson correlation, b - Spearman's correlation, * - Significant p value < 0.05				

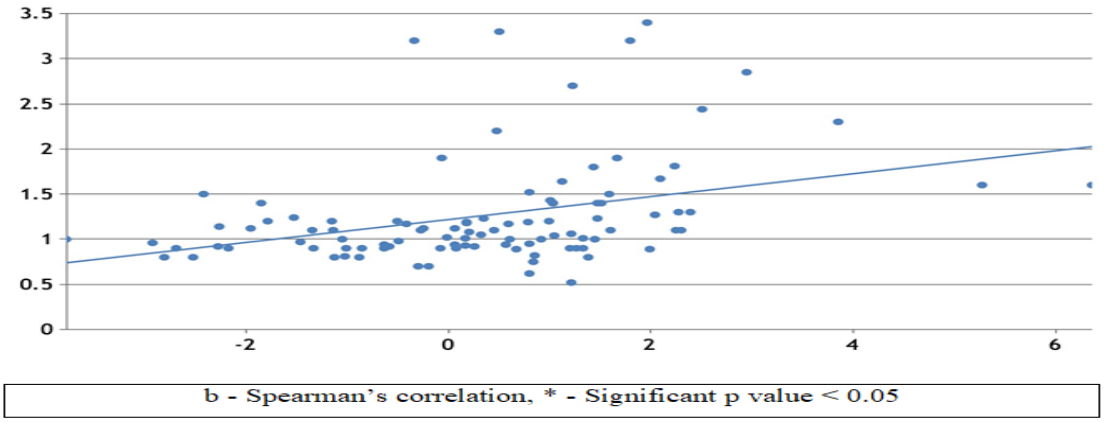

Figure 1: Correlation of HGI and serum creatinine levels in diabetic group (r = 0.4073, p = 0.00003[b*])

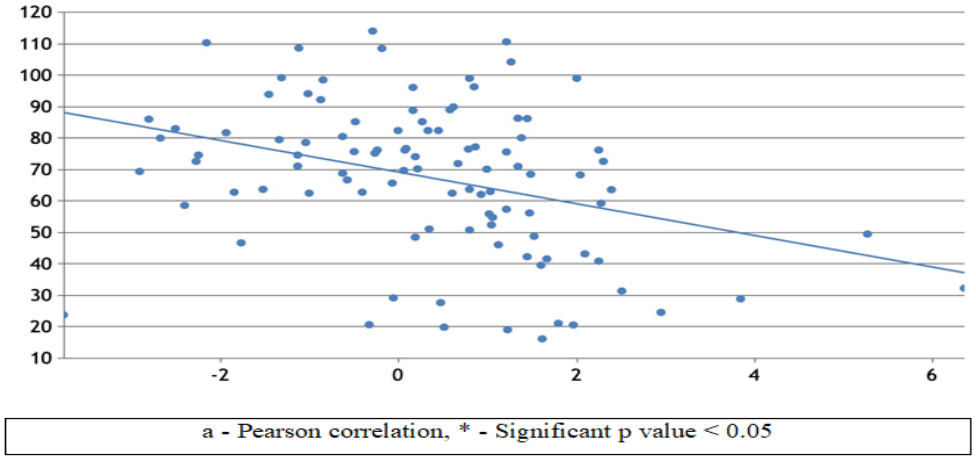

Figure 2: Correlation of HGI and eGFR levels in diabetic group (r = -0.3512, p = 0.0003[a*])

Discussion:

The two study groups namely diabetics and controls did not very much in their age group, thus the groups are age-matched. But males in the study population were found to have greater diabetes prevalence. Obesity is a diabetes risk factor and this is evident in our study population as higher BMI and WC were seen in the diabetics over controls [10]. The poor glycemic control was markedly seen in our diabetic subjects with higher FPG, 2-h PG and M-HbA1c levels.

There were greater individual variations in M-HbA1c and mean glucose levels, which were more pronounced in our diabetic cases than controls. Thus the P-HbA1c levels of diabetics were much altered than their M-HbA1c levels, which resulted in the greater HGI levels of diabetics than controls.

The change observed in the HGI levels of our study groups were not significant, unlike most previous evidences depicting distinctly raised HGI levels in pre-diabetes, diabetes and insulin resistance conditions than the normoglycemic subjects [11,12]. Our results clearly indicate a greater risk for overestimating diabetes diagnosis by using M-HbA1c alone. Also the utility of HGI to identify pre-diabetes and T2DM needs further evaluation in larger study population.

There are several biological factors causing discordance between individual levels of M-HbA1c and mean glucose levels. Some of them are genetic predispositions leading to variant glycation phenotypes, altered RBC lifespan, hemoglobinopathies, intracellular pH, redox state, glucose concentrations and presence of competing substrates for non-enzymatic addition to hemoglobin/proteins [5,6]. Like HGI, glycosylation gap (GG) is another index calculated from P-HbA1c levels regressed from fructosamine levels and is used to estimate such discordance in glycated proteins over mean glucose levels [13].

T2DM can lead to secondary dyslipidemia which in turn increase the risk for cardiovascular diseases. This is supported by the subtle but adverse changes in lipid profile of our diabetic subjects compared to controls.

But these adverse lipid changes did not correlate with the HGI or M-HbA1c levels in our diabetic subjects, thus questioning the predictive utility of HGI in diabetes associated cardiovascular disease risk. Our findings coincide with those of trials like DEVOTE study [9]. This is in contrary to many

previous trials highlighting otherwise the predictive role of HGI in major adverse cardiovascular events in diabetics [7,8]. These contrasting evidences may be due to the differences in ethnographic and biological characteristics of the study population.

Chronic diabetes is also associated with development of an array of microvascular and macrovascular systemic complications including nephropathy. This was also observed in our diabetic subjects who showed declining creatinine based eGFR levels than our control group. The increased HGI levels in our diabetic cases were strongly correlating with their increasing serum urea and creatinine levels, as well as with their declining eGFR levels. Such correlations were not observed with M-HbA1c levels in our diabetic subjects.

Our results are in concordance with those of Lin CH et al, the DCCT trial and the ADVANCE trail results, wherein HGI levels were successful in predicting the renal function decline, onset of chronic kidney disease (CKD), nephropathy in T2DM and type 1 diabetes mellitus patients [7,8,14]. Similarly, Cohen RM et al deduced the usefulness of higher GG levels in predicting the diabetic nephropathy risk [13].

Such correlations of higher HGI and GG levels to diabetic nephropathy, renal dysfunction, cardiovascular disease and other diabetic complications may be owed to the abnormal glycation process, though the mechanisms have not yet been understood completely. Selective glycation of targeted renal proteins is the suggested underlying mechanism for such adverse renal outcomes associated with elevated HGI levels. The chronic underlying glycemia due to insulin resistance could have accelerated the intracellular proteins' glycation process, which is also favoured in the pro-oxidant, pro-inflammatory cellular environment [7,8,14].

These cellular mechanisms predispose the diabetics as well as normoglycemic subjects with high HGI levels due to adverse glycation phenotypes towards developing the various microvascular and macrovascular systemic complications. This is evident form the studies by Nakasone Y et al and Fiorentino TV et al, that uphold the role of higher HGI levels in predicting kidney disease risk even in apparently healthy non-diabetic adults [15,16].

These findings suggest a possible utility of HGI over HbA1c, for predicting the declining renal function as a complication of T2DM, so that in future preventive therapies for glycemic control may be directed towards achieving the targeted lowering of HGI levels.

Conclusion:

Drastic changes were observed in glucose based regression levels of P-HbA1c and HGI in our diabetic group than the non-diabetic controls. Higher HGI levels correlated with increasing serum urea and creatinine levels as well as declining eGFR levels in our diabetic subjects. These findings suggest a possible role of HGI over HbA1c, in predicting the microvascular renal complications of T2DM.

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