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RESEARCH PAPER

Association of Hemoglobin Glycation Index with Non-alcoholic Fatty Liver Disease Diagnosed by Ultrasonogram in Non-diabetic Individuals

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent metabolic diseases worldwide. The hemoglobin glycation index (HGI) quantifies interindividual variations in glycated hemoglobin (HbA1c), and is associated with diabetic complications, and metabolic diseases.

Objective: To evaluate the association of Hemoglobin Glycation Index (HGI) with Non-alcoholic Fatty Liver Disease (NAFLD) in Non-diabetic individuals.

Methods: This cross-sectional analytical study was conducted at Sir Salimullah Medical College from March 2024 to February 2025. This study enrolled a total of 340 non-diabetic suspected cases of NAFLD with age range of 18-65 years attending the outpatient department of Hepatology, Sir Salimullah Medical College Mitford Hospital, Dhaka. The sampling technique was purposive. Based on the ultrasonogram findings, the study subjects were categorized into two groups: NAFLD, and non-NAFLD group. Hemoglobin glycation index (HGI) was calculated by subtracting the predicted value of HbA1c from the measured HbA1c level (HGI = measured HbA1c – predicted HbA1c) for all participants. A predicted value of HbA1c was calculated by inserting fasting plasma glucose concentration into simple linear regression equation (predicted HbA1c = 0.9616 × FPG mmol/L + 0.0963). Subjects were divided into low HGI group (HGI≤median) and high HGI group (HGI>median) using the median HGI as a cut-off value (- 0.38 %). HGI was compared between NAFLD, and non-NAFLD group by chi-square test. Risk of NAFLD in subjects with high HGI was calculated by odds ratio (OR). Using the median value as cut off point; performance of high HGI was determined for prediction of NAFLD with respect to sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. p value ≤0.05 was considered statistically significant.

Results: Among 340 participants, 141 study subjects (41%) were in the NAFLD group, and the rest 199 subjects (59%) belong to the non-NAFLD group. A significant association of high HGI with NAFLD (P value 0.00001) was observed, and subjects with high HGI found to have 6.85 times more risk to develop NAFLD (OR = 6.85, CI: 4.2 – 11.1). Receiver operating characteristics (ROC) curve analysis of high HGI (cut-off value- 0.38) for prediction of NAFLD showed area under curve (AUC) to be 0.697 and performance analysis of high HGI for detection of NAFLD showed sensitivity 63.8 %, specificity 79.8 %, PPV 75.2%, NPV 69.4% and accuracy 71.8 %.

Conclusion: There is significant association (OR = 6.85) of high hemoglobin glycation index (HGI) with nonalcoholic fatty liver disease (NAFLD) in non-diabetic individuals. High hemoglobin glycation index (HGI) as a diagnostic biomarker for prediction of nonalcoholic fatty liver disease (NAFLD) is not satisfactory because of its low sensitivity, poor specificity and low area under curve (AUC).

Keywords: Hemoglobin glycation index, Non-alcoholic Fatty Liver Disease, Non-diabetic individual

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a progressive liver illness ranging from hepatocellular steatosis to nonalcoholic steatohepatitis (NASH), which can develop into cirrhosis, and ultimately hepatocellular carcinoma.[1] It is considered as the most common liver disorder worldwide.[2] It correlates with metabolic disorders related to insulin resistance like type 2 diabetes mellitus, obesity, and metabolic syndromes.[3] Insulin resistance is an underlying cause of NAFLD in obese, and diabetic individuals as well

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as in non-obese people without diabetes.[4] Recently, Bangladesh is experiencing an increasing incidence of NAFLD because of altered food habits, and a sedentary way of living.[5] The prevalence of NAFLD in Bangladesh is 33.86%, and 71.18% of NAFLD cases here are present with diabetes. But the prevalence among non-diabetes has not been reported till date.[6] In the last decade, previous studies have shown that NAFLD is not only liver related disorder, but it also increases the risk of developing type 2 diabetes, cardiovascular disease (the major causes of death in NAFLD), chronic kidney disease, and certain extrahepatic malignancy such as colorectal cancer.[7]

Glycated hemoglobin (HbA1c) is a product of nonenzymatic glycation of the beta chain of adult hemoglobin. It is the gold standard for assessing glycemic status in an individual and represents the previous 2-3 months average blood glucose concentrations.[8] The blood glucose level, and interindividual biological variations contribute to HbA1c levels.[9] Different HbA1c values have been observed in patients with comparable mean plasma glucose levels.[3] Interindividual variability in the relationship between HbA1c, and underlying glucose levels may not be found only in individuals with pre-existing diabetes, but also in those with or without pre-diabetes.[10] Variety of factors like genetics, hemoglobinopathies, certain anemia, and disorders associated with accelerated red cell turnover such as malaria may affect HbA1c.[11]

Based on these limitations, Hempe, et al.[12] introduced the hemoglobin glycation index (HGI) in 2002 as a tool for quantifying glucose discrepancies, and HbA1c. HGI is the difference between measured HbA1c, and predicted HbA1c which is calculated by inserting plasma glucose levels into a population regression equation expressing the linear association between HbA1c, and circulating glucose levels.[12] It has been reported that a higher HGI value in type 2 diabetes patients is associated with diabetic complications, and greater mortality even in intensive treatment groups.[13] An association between HGI and the risk of cardiovascular diseases in such patients has also been demonstrated in other studies.[14] Even in non-diabetic individuals, elevated HGI levels correlate with higher risk of atherosclerosis, and coronary artery calcification.[15,16] Limited studies have been done to find out the association between HGI, and NAFLD in subjects without type 2 diabetes. This study explored the association between HGI and NAFLD in non-diabetic individuals of Bangladesh.

Materials and Methods

This cross-sectional study was conducted at the department of Biochemistry, Sir Salimullah Medical College (SSMC), Dhaka, Bangladesh, from March 2024 to February 2025. This study enrolled a total of 340 non-diabetes suspected cases of NAFLD attending the Outpatient Department of Hepatology, Sir Salimullah Medical college Mitford Hospital, Dhaka, Bangladesh. It was focused on adults aged between 18-65 years. A purposive sampling technique was used to select the study subjects. Participants with known cases of diabetes mellitus, heart failure, end stage renal disease, anemia, or haemoglobinopathies, malignant disease, acute, or chronic infection, HBV, or HCV infections, chronic alcoholism, and pregnant, and lactating women were excluded. Based on the ultrasonogram findings, the study subjects were categorized into two groups: NAFLD(n=141), and non-NAFLD(n=199) group.

The study variables were included age, fasting plasma glucose (FPG), HbA1c, and hemoglobin glycation index (HGI). Ethical clearance was obtained from the Institutional Ethics Committee of Sir Salimullah Medical College. All surveys were conducted after obtaining written informed consent from all subjects. Anthropometric variables were measured accordingly, and fasting blood sample was collected to measure biochemical variables. Fasting plasma glucose was measured using the glucose oxidase method.[17] HbA1c was measured using an immunoassay.[18] A predicted value of HbA1c was calculated by inserting fasting plasma glucose concentration into linear regression equation (predicted HbA1c = 0.9616 × FPG mmol/L + 0.0963). HGI was calculated by subtracting the predicted value of HbA1c from the measured HbA1c level (HGI = measured HbA1c – predicted HbA1c) for all participants.[19] According to the median HGI value (-0.38%) ; subjects were categorized into high HGI group (HGI > median) and low HGI group (HGI≤ median).[20] Statistical analysis was done by using SPSS version 25. Mean ± standard deviation (SD) was used to represent the quantitative data with approximately normal distribution. Categorical variables were described by frequency and percentage. Chi-square ($\chi 2$) test was done to determine the association between categorical variables. The odds ratio (OR) was used to determine

the risk of NAFLD in subjects with high HGI. Receiver operating characteristics (ROC) curve analysis and diagnostic performance test were done to determine the efficacy of high HGI for prediction of NAFLD. A *p* value of ≤0.05 was considered statistically significant.

Results

A total of 340 non-diabetic subjects were included in this study. Among the 340 study subjects, 141 (41%) were grouped as NAFLD, while the remaining 199 (59%) belonged to the non-NAFLD group (Table I). The mean age of the NAFLD group was 40.95 ± 8.63 years, which was higher compared to 37.63 ± 8.52 years in the non-NAFLD group. Among the 141 NAFLD subjects, 55 (39.1 %) were males, and 86 (60.9 %) were females, whereas in the 199 non-NAFLD subjects, 52 (26.1 %) were males, and 147 (73.9 %) were females (Table II).

Table I: Grouping of study subjects (n = 340)

Group	Frequency (%)
NAFLD	141 (41 %)
non - NAFLD	199 (59 %)

Table II: Age and gender distribution of study subjects (n = 340)

Parameters	NAFLD (n = 141)	non – NAFLD (n = 199)
Age (mean ± SD)	40.95 ± 8.63	37.63 ± 8.52
Male	55 (39.1%)	52 (26.1 %)
Female	86 (60.9 %)	147 (73.9 %)

Based on hemoglobin glycation index (HGI) values, 167 subjects (49.1%) were categorized in the high HGI group (- 0.39 to 0.69 %), while 173 subjects (50.8%) were categorized in the low HGI group (- 1.38 to – 0.38 %) (Table III).

Table III: Categorization of study subjects according to hemoglobin glycation index (HGI) value (n = 340)

HGI	Status	Frequency (%)
(- 0.39 to 0.69) %	High	167 (49.1 %)
(-1.38 to - 0.38) %	Low	173 (50.8 %)

The risk of NAFLD was significantly higher among the individuals with a high HGI compared to those with a low HGI, and high HGI was 6.85 times risker to have NAFLD (OR: 6.85, CI: 4.2 – 11.1, *p* = 0.00001) (Table IV).

Table IV: Risk of NAFLD among the individuals with high HGI (n = 340)

Group		NAFLD Present No. (%)	NAFLD Absent No. (%)	Total	(OR) Odds Ratio	95% CI (Confidence Interval)	χ^2 value	*p*-Value
HGI	High	106	61	167	6.85			
	Low	35	138	173		4.2-11.1	65.46	0.00001
	Total	141	199	340				

The Receiver Operating Characteristic (ROC) curve of Hemoglobin Glycation Index (HGI) for the prediction of NAFLD, demonstrated an Area Under the Curve (AUC) of 0.697.

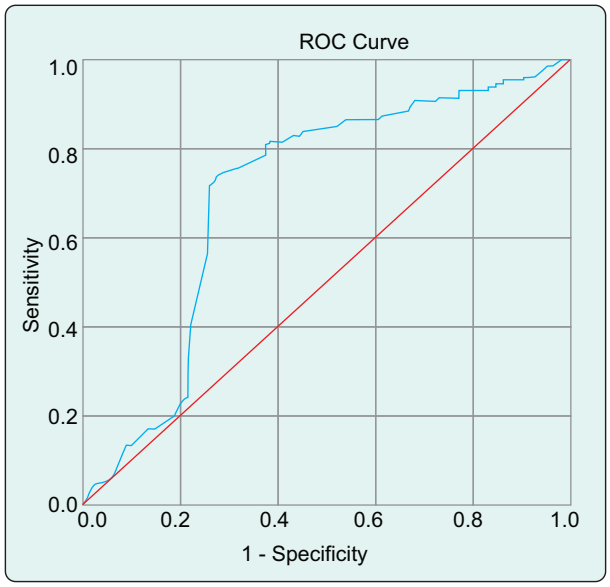

Figure 1: Receiver Operating Characteristic (ROC) curve of HGI for prediction of NAFLD (AUC: 0.697)

The performance of high HGI using a cut-off value of 0.38 for prediction of NAFLD, demonstrated a sensitivity of 63.8 %, specificity of 79.8 %, positive predictive value (PPV) of 75.2 %, negative predictive value (NPV) of 69.4 %, and overall accuracy of 71.8 %. (table-V)

Table V: Performance of high HGI (cut-off value – 0.38) for prediction of NAFLD

HGI	Sensitivity	Specificity	PPV	NPV	Accuracy
	63.8 %	79.8%	75.2%	69.4%	71.8%

Discussion

It was observed that, 141 (41 %) subjects have NAFLD where 39.1 % were males, and 60.9 % were females.

Remaining (199, 59 %) were found did not have NAFLD (26.1 % male and 73.9 % female). Overall, females were more prevalent in both NAFLD, and non-NAFLD groups. In consistent with this study, a Bangladeshi study showed that female was more frequent in NAFLD group, and control group with male female ratio was 1:1.7 and 1:1.8 respectively.[2] This finding was also similar in other Bangladeshi studies.[21] In contrast to this study, the prevalence of NAFLD is higher in males (40%) compared to females (26%) found in previous studies.[1] An interesting study showed that women had a significantly higher prevalence of NAFLD compared with men, but severity of NAFLD is higher in males.[22] This is due to males had thicker visceral adiposity, lower levels of serum adiponectin and higher metabolic risk factors such as insulin resistance, abdominal obesity and metabolic syndrome than females. The mean age was higher in the NAFLD group (40.95 ± 8.63 years) compared to the non-NAFLD group (37.63 ± 8.52 years). Similar findings were observed in the other studies.[2]

According to the median cut-off value of HGI - 0.38 %, in high HGI group 167 (49.1%) subjects were found, and the rest of 173 (50.8%) subjects were found in low HGI group. This study demonstrated that high HGI was significantly associated with NAFLD, and high HGI was 6.85 times riskier to have NAFLD. The prevalence of NAFLD increased significantly with increasing HGI, and HGI was an independent risk factor for NAFLD observed in previous studies.[3] Similar findings were observed in the other studies.[23]

Receiver Operating Characteristics (ROC) curve analysis of high HGI (cut-off value of HGI - 0.3895) for prediction of NAFLD showed that Area Under Curve (AUC) of 0.697 (95% CI: 0.639 - 0.755), achieving a sensitivity 63.8 %, and specificity 79.8 %. The diagnostic accuracy was 71.8 %. Due to its poor performance and low AUC, high HGI cannot be considered a reliable diagnostic marker for detection of NAFLD.

The pathophysiological mechanism involved how HGI to progress NAFLD is still unclear. Intracellular glucose levels are greater in high HGI individuals than in comparatively low HGI individuals. Excess intracellular glucose causes the release of harmful compounds that might damage the liver. It has been found that advanced glycation end products (AGEs) are reflected in the HGI. The normal structure and function of proteins are altered by AGEs, which can lead to pathogenic alterations in the liver.[24]

Conclusion

The study highlights the significant association of high Hemoglobin glycation index (HGI) with Nonalcoholic Fatty Liver Disease (NAFLD) in non-diabetic individuals. High hemoglobin glycation index (HGI) as a diagnostic biomarker for prediction of Nonalcoholic Fatty Liver Disease (NAFLD) is not satisfactory because of its poor sensitivity, poor specificity and low area under curve (AUC).

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