ORIGINAL ARTICLE

Hemoglobin glycation index and triglyceride-glucose index are related to diabetic nephropathy

El índice de glucosilación de la hemoglobina y el índice de triglicéridos-glucosa están relacionados con la nefropatía diabética

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Abstract

Objective: *Diabetic nephropathy (DN) is a significant complication of diabetes. Despite strict management of fasting plasma glucose (FPG), DN may progress to end-stage renal disease. HbA1c, the best biomarker for glycemic management, may differ in similar FPG. Hemoglobin glycation index (HGI) = HbA1c as determined minus HbA1c as predicted. The triglyceride-glucose index (TGI) is found to detect insulin resistance and correlates with DN. The aim of this study is to see the association of TGI and HGI with diabetic nephropathy in type 2 diabetes patients.* **Method***: 234 patients with type 2 diabetes were analyzed retrospectively.* **Results:** *87 (37.2%) of 234 patients were male, and the mean age was 57.2 ± 11.1 years. 76 of the patients had DN. HGI and TGI were significantly higher in the DN group (2.59 ± 1.7 vs. 1.18 ± 0.34; p = 0.00 and 9.9 ± 0.7 vs. 9.7 ± 0.7; p = 0.024). In logistic regression analysis, microalbuminuria was associated with TGI (OR = 3.35, 95% CI, 1.778- 6.32, p = 0.01) and HGI (OR = 2.579, 95% CI, 1.89-3.516, p = 0.00).* **Conclusions:** *In conclusion, TGI and HGI were independently associated with diabetic nephropathy. These markers may be useful in DN, especially in anemic individuals, since anemia might affect HbA1c levels.*

Keywords: *Hemoglobin glycation index. Triglyceride glucose index. Diabetic nephropathy.*

Resumen

Objetivo: *La nefropatía diabética (ND) es una complicación importante de la diabetes. A pesar del manejo estricto de la glucosa plasmática en ayunas (GPF), la ND puede progresar a enfermedad renal terminal. La hemoglobina glucosilada (HbA1c), el mejor biomarcador para el manejo glucémico, puede diferir en una GPF similar. Índice de glucosilación de hemoglobina (HGI) = HbA1c según lo determinado menos HbA1c según lo previsto. Se ha encontrado que el índice de triglicéridos-glucosa (TGI) detecta la resistencia a la insulina y se correlaciona con la ND. El objetivo de este estudio es ver la asociación de TGI y HGI con ND en pacientes con diabetes tipo 2.* **Método:** *Se analizaron retrospectivamente 234 pacientes con diabetes tipo 2.* **Resultados:** *Ochenta y siete (37.2%) de 234 pacientes eran varones, y la edad media fue de 57.2 ± 11.1 años. Setenta y seis pacientes tenían ND. HGI y TGI fueron significativamente mayores en el grupo ND (2.59 ± 1.7 vs 1.18 ± 0.34; p = 0.00 y 9.9 ± 0.7 vs 9.7 ± 0.7; p = 0.024). En el análisis de regresión logística, la microalbuminuria se asoció con TGI (odds ratio [OR]: 3.35; IC95%: 1.778-6.32; p = 0.01) e HGI (OR: 2.579; IC95%: 1.89-3.516; p = 0.00).* **Conclusiones:** *En conclusión, TGI y HGI se asociaron de forma independiente con la ND.*

Palabras clave: *Índice de glucosilación de la hemoglobina. Índice de glucosa en triglicéridos. Nefropatía diabética.*

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Introduction

Diabetic nephropathy (DN) is one of the most significant consequences of diabetes, affecting about one-third of diabetes patients[1]. Because the mechanisms underlying DN development are complex, therapeutic outcomes are poor. Strict fasting plasma glucose (FPG) and blood pressure management are insufficient to prevent mortality and the progression of DN into end-stage renal disease[2,3]. Many processes have a role in the start and progression of DN, including oxidative stress, the angiotensin II system, and inflammation[4].

Despite the fact that HbA1c is regarded as the most reliable glycemic management biomarker, studies have shown that there are considerable disparities between HbA1c and mean blood glucose levels. Because of changes in glucose metabolism and hemoglobin glycation rate, patients with comparable blood glucose levels may have different HbA1c values[5,6]. Hemoglobin glycation index (HGI) was calculated as observed HbA1c minus predicted HbA1c. Predicted HbA1c is calculated by linear regression equation reflecting the relationship between baseline HbA1c and FPG. Hempe et al.[7] recommend using the HGI to compare mean blood glucose levels to HbA1c readings. HGI was found to be related to macrovascular problems[8] and diabetic nephropathy[9].

Previous research has shown that the triglyceride-glucose index (TGI), is an excellent tool for detecting insulin resistance in both diabetic and non-diabetic patients[10,11]. Furthermore, previous research has linked TGI to diabetic nephropathy[12].

The goal of this research is to see the association of TGI and HGI with diabetic nephropathy in people with type 2 diabetes.

Method

This was a retrospective analysis of 234 patients with type 2 diabetes who attended an internal medicine outpatient clinic between January and December of 2022.

Moreover, it was done in accordance with the Helsinki Declaration. Because the research was conducted retrospectively, informed consent was not obtained. The following criteria were used to determine study eligibility: (1) patients with a diagnosis of type 2 diabetes according to the World Health Organization criteria; (2) ≥ 18 years old; (3) have had diabetes for at least a year; and (4) had no documented ketoacidosis in the 3 months before enrolment. Participants were excluded if they had a febrile or infectious illness, obstructive uropathy, severe heart failure, stroke, liver disease, cancer, autoimmune disease, and pregnancy. An albumin excretion rate (AER) of 30 mg/gr was discovered in at least two of three consecutive spot urine albumin-creatinine ratios to diagnose DN. Albuminuria in non-diabetic renal disease is another exclusion criterion for patients with DN. The files included all biochemical results and HbA1c levels. TGI was calculated as ln [fasting triglycerides (mg/dL) × FPG (mg/dL)/2]. HGI was calculated as observed HbA1c minus predicted HbA1c. The linear regression equation reflecting the relationship between baseline HbA1c and FPG in our cohort was HbA1c (%) = 5.69 + 0.018 FPG (mg/dL) for the 234 individuals. The predicted HbA1c for each patient in our study was calculated from this equation.

A statistical investigation using SPSS 25.0 was used to analyze the data (SPSS Inc., Chicago, IL, USA). For continuous variables, data are reported as the mean standard error, or median (interquartile range), and for categorical variables, as percentages. The student's t-test and Mann–Whitney U-test were used to compare the two groups (DN vs. non-DN). A univariate regression analysis was used to examine the potential risk factors for the development of DN, and a binary logistic regression multivariable analysis with DN categorized as a binary variable (presence or absence of DN) was used to assess the associations between the measured risk factors and DN. A P-value of 0.05 was used to establish statistical significance.

Results

A total of 234 patients were involved in the study, of whom 87 (37.2%) were male. The mean age was 57.2 ± 11.1 years and the mean DM vintage was 9.7 ± 7.5 years. 132 (56.4%) of the patients had HT, and 123 (52.6%) of the patients had hyperlipidemia. The mean BMI was 31.05 ± 7.19 kg/m^2. The mean FBG was 215 ± 97.7 mg/dL, mean HbA1c was 9.7 ± 2.5. The mean HGI was 1.7 ± 1.01 and mean TGI was 9.75 ± 0.74 (Table 1).

The patients were grouped in 2 with respect to the presence of microalbuminuria. 76 of the patients had microalbuminuria (MA), while 148 did not. The patients with MA were older (60.6 ± 10.2 vs. 52.2 ± 11.1; p = 0.00). BMI was higher in the MA group (32.4 ± 9.1 vs. 30.3 ± 5.7; p = 0.036) and systolic blood pressure (SBP) was

Table 1. Baseline characteristics

Demographics	n = 234
Males, n (%)	87 (37.2%)
Age, years	57.2 ± 11.1
DM vintage, years	9.71 ± 7.5
HT, n (%)	132 (56.4)
Hyperlipidemia, n (%)	123 (52.6%)
BMI, kg/m^2	31.05 ± 7.19
SBP, mm/hg	124.4 ± 14.1
DBP, mm/hg	76.8 ± 11.3
Hemoglobin, g/dL	13.7 ± 6.2
CRP, gr/dL	2.19 ± 1.45
Ferritin, ng/dL	95.6 (4.2-1191)
FBG, mg/dL	215 ± 97.7
Serum albumin, g/dL	4.3 ± 0.5
GFR, mL/min	87.8 ± 26.3
Serum total cholesterol, mg/dL	193.8 ± 48.9
Serum triglycerides, mg/dL	200.9 ± 107.1
HbAıc	9.7 ± 2.5
HGI	1.7 ± 1.01
TGI	9.75 ± 0.74

DM: diabetes mellitus; HT: hypertension; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HGI: hemoglobin glycation index; TGI: triglyceride glucose index; GFR: glomerular filtration rate; CRP: C-reactive protein.

Table 2. Comparison of patients in terms of microalbuminuria

Demographics	MA(-) (n = 148)	MA(+) (n = 76)	p
Males, n (%)	54 (36.5%)	33 (38.4%)	0.774
Age, years	52.2 ± 11.1	60.6 ± 10.2	0.00
DM vintage, years	9.5 ± 7.5	10.1 ± 7.6	0.466
HT, n (%)	78 (52.7%)	54 (62.8%)	0.134
Hyperlipidemia, n (%)	77 (52%)	46 (53.8%)	0.829
BMI, kg/m^2	30.3 ± 5.7	32.4 ± 9.1	0.036
SBP, mm/hg	123 ± 14.5	126.9 ± 13.2	0.040
DBP, mm/hg	76.5 ± 10.4	77.3 ± 12.8	0.659
Hemoglobin, g/dL	14.1 ± 1.7	13.0 ± 1.8	0.053
CRP, gr/dl	2.02 ± 0.9	2.5 ± 1.9	0.017
Ferritin, ng/dl	80.6 (4.2-489)	121.3 (10-1192)	0.013
FBG, mg/dl	210.1 ± 92.8	224 ± 105.5	0.42
Serum albumin, g/dL	4.4 ± 0.4	4.2 ± 0.7	0.014
GFR, ml/min	92.7 ± 24.5	78.9 ± 27.3	0.00
Serum total cholesterol, mg/dL	189.7 ± 42.3	200.8 ± 58.2	0.182
Serum triglycerides, mg/dL	187.8 ± 96.7	223.3 ± 120.1	0.014
HbAıc	9.6 ± 2.4	9.8 ± 2.6	0.069
HGI	1.18 ± 0.34	2.59 ± 1.7	0.00
TGI	9.7 ± 0.7	9.9 ± 0.7	0.024

DM: diabetes mellitus; HT: hypertension; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HGI: hemoglobin glycation index; TGI: triglyceride glucose index; GFR: glomerular filtration rate; CRP: C-reactive protein.

increased MA group (126.9 ± 13.2 vs. 123 ± 14.5; p = 0.040). CRP and ferritin were increased in the MA group (Table 2). FBG and HbA1c were statistically similar between groups (Table 2). Serum triglyceride was increased in the MA group (223.3 ± 120.1 vs. 187.8 ± 96.7; p = 0.014). HGI and TGI were significantly higher in the MA group (2.59 ± 1.7 vs. 1.18 ± 0.34; p = 0.00 and 9.9 ± 0.7 vs. 9.7 ± 0.7; p = 0.024) (Table 2).

Table 3 shows the multivariate-adjusted odds ratios for microalbuminuria outcome measures. Multiple logistic regression adjusted for potential confounders demonstrated that microalbuminuria was associated with age (odds ratio [OR] = 1.064, 95% confidence interval [CI], 1.027-1.100, p = 0.001), SBP (common OR = 1.034, 95% CI, 1.005-1.065, p = 0.022), TGI (OR = 3.35, 95% CI, 1.778-6.32, p = 0.01) and HGI (OR = 2.579, 95% CI, 1.89-3.516, p = 0.00). HbA1c was statistically related to the development of DN (OR 1.6, 95% CI, 1.85-2.1, p = 0.003) (Table 3).

Discussion

Individuals with DN showed significantly higher levels of metabolic syndrome markers such as BMI, SBP, triglycerides, and CRP, according to this research. Although HbA1c levels did not differ across groups, the DN group had substantially higher HGI and TGI levels. A multivariate logistic regression analysis found that the most significant predictors of DN were age, systolic blood pressure, HGI, TGI, and Hba1c.

Diabetic nephropathy (DN) is a frequent and serious complication that increases the risk of both mortality and morbidity in diabetic individuals[1]. The number of diabetics in the United States who started therapy for end-stage renal disease (ESRD) grew from 40,000 to more than 50,000 between 2000 and 2014[13].

Previous study has shown that the TGI is a trustworthy and accurate predictor of metabolic syndrome,

Table 3. Logistic regression analysis

Multiple logistic regression		
Predictors	**OR (95% CI)**	**p**
HGI	2.579 (1.89-3.516)	0.000
HbA1c	1.6 (1.85-2.1)	0.003
Age	1.064 (1.027-1.10)	0.001
SBP	1.034 (1.005-1.065)	0.022
TGI	3.35 (1.778-6.321)	0.000

95% CI: 95% confidence interval; HGI: hemoglobin glycation index; TGI: triglyceride glucose index; SBP: systolic blood pressure.

insulin resistance[14-16], and macrovascular disease[17-19]. In this study, we concluded that TGI serves as an independent indicator for the development of DN.

Prior research has shown the significance of insulin resistance in the progression of DN. Increased renal vascular permeability is the mechanism through which insulin resistance induces glomerular hyperfiltration. The result is an increase in pressure inside the glomeruli[20]. Among the likely pathophysiological mechanisms underlying the association between insulin resistance and DN include inflammation, oxidative stress, metabolic acidosis, and lipotoxicity[21-24].

Multiple studies have shown that dyslipidemia has a role in the advancement of renal failure in both type 1 and type 2 diabetes[25,26]. Prior research discovered a relation between DN and HOMA-IR, an additional biomarker of insulin resistance. Over the course of a prospective cohort study spanning 5 years, researchers identified a correlation between baseline HOMA-IR and the start of microalbuminuria[27]. Endothelial cell damage in microalbuminuria, according to Deckert et al., causes considerable vascular damage by reducing endothelial lipoprotein lipase levels[28]. This injury causes hypertriglyceridemia by increasing plasma triglyceride levels. The current findings are consistent with previously published studies, which makes sense given that TGI is a marker of insulin resistance.

It has been postulated that insulin treatment, in addition to blood glucose and blood pressure, may have a role in the development of nephropathy[29]. Kim et al.[30] identified unique relationships between fasting plasma insulin levels, systolic blood pressure, and microalbuminuria. Individuals who have high plasma glucose levels have a combination of abdominal obesity, high blood pressure, elevated lipid levels, and metabolic syndrome[31,32]. According to the present study, the TGI is more sensitive than the metabolic syndrome-related indicators in DN[33], which is consistent with earlier results.

Another notable result from this research is that the glycation index was found to be higher in the DN group despite HbA1C being comparable in both groups. Both of these features were linked to the development of diabetic nephropathy in a regression analysis.

The HGI illustrates the link between HbA1c and plasma glucose levels[11]. The HGI is the difference between the actual HbA1c and the value predicted by a simple linear model that predicts HbA1c from FPG concentration for each patient in a study population, i.e., the residual from the fitted linear regression line for each patient in a study population. The HGI is calculated by subtracting the observed HbA1c from the value predicted by the basic linear model.

Previous studies[10,34-36] have shown that the HGI has a consistent value throughout a broad range of blood glucose concentrations, as well as a uniform distribution and stability over time. According to the results of the DCCT study, a high HGI was associated with an increased risk of developing retinopathy and nephropathy in type 1 diabetes patients[6].

A non-enzymatic mechanism that glycates hemoglobin is the Maillard reaction. The interaction of reducing sugars with terminal amines is definitely required for the development of advanced glycation end products. The pathophysiology of advanced glycation end products has been linked to diabetic complications, aging, and Alzheimer's disease[37]. The DCCT findings, which link biological variation in HbA1c to microvascular complications, suggest that the mechanisms that cause biological variation in non-enzymatic hemoglobin glycation may also influence a patient's susceptibility to diabetes complications[38-40]. The non-enzymatic glycation of hemoglobin is regulated by intracellular glucose as well as factors that affect the hemoglobin's capacity to bind glucose. The pH of the intracellular environment, the concentration of 2, 3-bisphosphoglycerate, and the activity of glycolytic enzymes all impact hemoglobin glycosylation[41,42]. There is no association between erythrocyte survival and HGI; however, depending on creatinine levels, erythrocyte survival may effect HbA1c levels[11]. The risks of having consistently high glucose levels are well known, but the impact of non-glucose factors on HbA1c biological variation is little understood. This is due to the fact that HbA1c is a measure of blood glucose levels over time. Despite the fact that medication

and lifestyle adjustments may bring blood glucose levels as close to normal as possible, lowering blood glucose may not be enough to avoid retinopathy in DCCT patients due to the higher risk of retinopathy in individuals with low BG but a high HGI(6). Despite the fact that the underlying mechanism is not fully understood, further therapy to correct the variation indicated by HGI may be required. Understanding these pathways might help to generate new therapeutic options and patient-specific treatment regimens.

The current research has a number of limitations. To begin with, the total number of patients is small. Second, since the inquiry was done retrospectively, the indices were created using the experiment's starting values. We don't have any data on how these factors have changed over time. Second, since participants in medical checkups at a certain hospital are chosen at random, it is possible that they may not accurately reflect the whole population and are subject to the effects of natural selection bias.

Conclusion

We discovered that a greater TGI and HGI were detected in diabetic nephropathy. These markers may be useful in the determination of metabolic control and progression to DN, especially in anemic individuals since anemia might affect HbA1c levels. More research with prospective design is needed to determine whether or not these indices have a role in the occurrence and progression of diabetic microvascular problems.

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Conflicts of interest

The author declares no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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