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Association between Glycated Haemoglobin Index and Triglyceride-Glucose Index in a Non-Diabetic Cohort and its Correlation with Insulin Resistance

Associação entre o índice de hemoglobina glicada e o índice triglicerídeos-glicose em uma amostra de indivíduos sem diabetes e sua relação com resistência insulínica

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Abstract
Introduction: *elevated triglyceride/glucose index (TyG) and glycation of haemoglobin index (HGI) have been linked to complications associated with insulin resistance (IR).* ***Aim:*** *this study evaluated the association between TyG and HGI in non-diabetic individuals and its relationship with IR.* ***Methods:*** *a cross-sectional study was conducted with 32 non-diabetic subjects. Age, sex, body mass index, and laboratory data (triglycerides, glucose, HbA1c, and insulin) were analysed. TyG index, HOMA-IR, and HGI were calculated. Simple and multivariate linear regressions, ANOVA, and Pearson's correlations were performed.* ***Results:*** *multivariate linear regression revealed a significant association between TyG and HGI ($p < 0.001$), confirmed by T-test. A strong positive correlation was observed with a Pearson coefficient of 0.98.* ***Conclusion:*** *TyG, HGI, and IR demonstrated significant association in the study sample. This suggests both indices are reliable IR and glucose metabolism markers, potentially independent of fasting plasma glucose and other measured variables.*
Keywords: *Glycated Haemoglobin Index; Triglyceride-Glucose Index; Insulin Resistance.*

Resumo
Introdução*: estudos têm mostrado que elevações do índice triglicerídeo/glicose (TyG), bem como do índice de glicação da hemoglobina (IGH), estão associadas a várias complicações relacionadas à resistência à insulina (RI).* ***Objetivo****: avaliar a associação entre índice TyG e IGH em uma amostra de indivíduos sem diabetes e sua relação com RI.* ***Methodology****: foi conduzido um estudo transversal com 32 indivíduos não diabéticos. As variáveis analisadas incluíram idade, gênero, índice de massa corporal e dados laboratoriais (triglicerídeos, glicose, HbA1c e insulina). Calculamos o índice TyG, HOMA-IR e IGH. Análises de regressão linear simples e multivariada foram realizadas, além de ANOVA e correlação de Pearson entre as variáveis.* ***Resultados****: a análise de regressão linear multivariada da amostra analisada revelou uma correlação significativa entre o índice TyG e IGH, o que foi confirmado pelo teste T. Os resultados indicaram uma forte correlação positiva entre o índice TyG e IGH, com um coeficiente de correlação de Pearson de 0,98.* ***Conclusão****: o IGH, índice TyG e RI mostraram uma associação significativa na amostra analisada. Isso sugere que ambos os índices (IGH, índice TyG) são confiáveis na avaliação da RI e do metabolismo da glicose, e podem ser marcadores de risco independentes da glicose plasmática em jejum e das outras variáveis avaliadas neste estudo.*
Palavras-chave*: Índice de glicação da hemoglobina; Índice triglicerídeo-glicose; Resistência à insulina.*

INTRODUCTION

The haemoglobin A1c (HbA1c) test is commonly used to measure a person's average blood glucose concentration over the past 2-3 months. However, recent research suggests that differences in blood glucose levels alone[1] cannot fully explain the levels of HbA1c in different populations. Other factors, such as pH and erythrocyte turnover, can influence HbA1c levels[2]. In addition, certain individuals and racial groups consistently have HbA1c levels that are higher or lower than expected based on their blood glucose levels[3]. This indicates that factors beyond blood glucose, including inflammation and oxidative stress, may impact HbA1c levels[4]. Consequently, using HbA1c as a tool for diagnosing and managing diabetes can be challenging.

The haemoglobin glycation index (HGI) has been developed to address this issue. The HGI utilizes a population-based linear regression equation to estimate a predicted HbA1c based on plasma glucose values. By

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subtracting the measured HbA1c from the predicted HbA1c, the HGI is calculated: HGI = measured HbA1c – predicted HbA1c[5]*. This approach allows for evaluating inter-individual variations in HbA1c, considering various conditions other than blood glucose levels. In fact, studies have shown that HGI is not only a risk factor for cardiovascular disease but also associated with inflammation and other risk factors*[6]*.*

Another reliable indicator of insulin resistance (IR) is the TyG index, which has been validated against the hyperinsulinemic-euglycemic clamp test[7] *and the Homeostatic Model Assessment for IR (HOMA-IR)*[8]*. In a manuscript published in 2010 by Guerrero Romero F et al., the credibility of the TyG index as a marker of IR was confirmed*[9]*. The TyG index was initially proposed by Simental-Mendia et al.*[10] *in 2008, who assessed a sample of healthy individuals in a cross-sectional study. Subsequently, the TyG index has been used to evaluate IR, atherosclerosis, and hepatic fatty infiltration in healthy individuals*[11,12]*.*

Therefore, this study aimed to investigate the relationship between the TyG index and HGI in a sample of individuals without diabetes and assess its association with IR.

METHODS

A cross-sectional study was conducted with individuals without diabetes. The variables analyzed included age, gender, height, body mass index (BMI), abdominal waist, laboratory data (triglycerides, glucose, HbA1c, and insulin), TyG index, HOMA-IR, and HGI.

The study was conducted according to the Declaration of Helsinki, and participants signed informed consent. The National Commission for Research Ethics (CONEP) approved the project (registry number: 2.464.513).

Biochemical Tests

Plasma insulin, triglyceride and fasting glucose levels were determined using the VITROS® 5600 Integrated System. The HOMA-IR was evaluated using fasting plasma glucose (FPG) level and fasting insulin level. According to the manufacturer's instructions, the HbA1c was measured using a Roche Co-bas c501 automatic analyzer using turbidimetric inhibition immunoassay.

Calculating the HOMA-IR

HOMA-IR was calculated using fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5.

Generally, optimal insulin sensitivity is achieved when your HOMA-IR is less than 1. Levels above 1.9 indicate early IR, while levels above 2.9 indicate significant IR[7]*.*

Calculating the TyG index

The TyG index was calculated using the lipid profile and FPG data, based on the formula TyG = Ln [Tg (mg/dL) x Glycemia (mg/dL) / 2], where Ln is the neperian logarithm[8]*.*

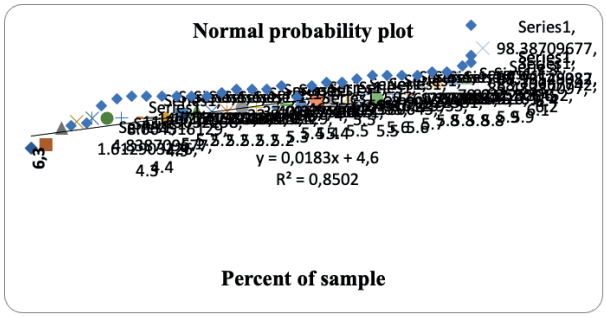
Individuals with an index of 3.7 (3.5, 3.9) probably do not have IR[10]*.*

Calculating the HGI

The data obtained from the sample were utilized to determine the linear correlation between FPG and HbA1c in the study populace. The equation represented this: HbA1c = (0.0183 × FPG (mg/dL)) + 4.6. Further, HGI was calculated by deducting the predicted HbA1c value from the observed HbA1c value (Figure 1)[5]*.*

Each individual was then assigned to low, moderate, or high HGI subgroups based on weighted HGI tertile (33.3%) cut points (low HGI < −1.5; n = 22; moderate HGI, −0.6–1.5; n = 6; high HGI > 0.6; n = 4).

Figure 1 – *Linear correlation between FPG and HbA1c*



Statistical Analysis

The data were analyzed using Excel and R 3.1.1, and normality was determined based on parameters such as mean, median, and standard deviation. Simple and multivariate linear regression analysis ANOVA and Pearson's correlation between variables were also performed.

A significance level of P < 0.05 was adopted for all variables.

RESULTS

Data from 72 patients were included, 48.60% female and 51.40% male; mean age of 45.31 ± 13.72 years; weight 88.52 ± 18.27 Kg, BMI 32.25 ± 5.73 Kg/m^2*, and waist circumference 99.68 ± 14.52cm.*

Correlation between TyG index and HGI

The multivariate linear regression analysis of the sample analyzed revealed a correlation between the TyG index and HGI, which the T-test confirmed. The results are displayed in Table 1, clearly illustrating this correlation.

Table 1 – *Correlation among TyG index, HGI and HOMA-IR*

	Coefficients	Standard error	Stat t	valor-P
HGI	1,404951392	2,365706072	0,015938825	0,005719531
TyG	0,028110626	0,516966214	0,054376138	0,007008372
HOMA	-0,029796592	0,035798059	-0,83235217	0,004120124

The results indicated a strong positive correlation between the TyG index and HGI, with a Pearson correlation coefficient 0.98.

DISCUSSION

We used the HGI to test the hypothesis that changes in HbA1c associated with the TyG index in a without diabetes adult population are reliable indices for assessing IR and glucose metabolism. These indices may also serve as independent risk markers, irrespective of FPG levels and other variables considered in this study. It is worth noting that since 2010, the American Diabetes Association has approved HbA1c for diagnosing diabetes and detecting pre-diabetes[13].

The HGI calculates HbA1c fluctuations based on variables beyond blood glucose concentration alone[14]. Advanced glycation end products (AGEs) contribute to IR, and increased HGI has been linked to elevated AGE levels[15]. Studies demonstrated that individuals with high HGI exhibit lower insulin sensitivity than those with normal or low HGI, regardless of body mass index (BMI), sex, or age[16]. Moreover, research has shown that individuals without diabetes with elevated HGI face an increased risk of atherosclerosis, coronary heart disease, and chronic kidney disease[17-19], while the ACCORD study[6] revealed the predictive potential of HGI for cardiovascular risk.

Our study found a statistically significant correlation between elevated HGI and HOMA-IR, indicating an association. The TyG index, often employed as a substitute indicator to evaluate IR, is widely recognized for its reliability[20]. Early studies conducted by Abbasi et al. and Simental-Mendía et al.[21,22] established the usefulness of the TyG index as a readily measurable marker for both metabolic syndrome and IR. Its calculation involves basic laboratory parameters such as glucose and triglycerides. Furthermore, the TyG index is more effective than surrogate markers like HOMA-IR in predicting IR when compared to direct measurement methods like the hyperglycemic clamp method[23].

However, a recent systematic review revealed evidence of varying quality regarding the effectiveness of the TyG marker as a surrogate biomarker for diagnosing IR. This calls for additional validation and establishing standardized cut-off values before implementing this marker in clinical practice[24]. Despite this systematic review, our study corroborates several published manuscripts by presenting a statistically significant association between elevated TyG levels and HOMA-IR.

Our study investigated the association between the TyG index, HGI, and insulin resistance (IR), revealing a significant correlation among these parameters in the analyzed sample. These results indicate that both indices are reliable for assessing IR and glucose metabolism and can be used interchangeably in clinical practice. Moreover, these findings provide valuable insights into the pathophysiology of metabolic disorders, such as diabetes, obesity, and cardiovascular diseases, where IR plays a pivotal role.

Supporting the notion that the TyG index and HGI are reliable indicators for diagnosing IR, this study emphasizes the importance of early identification of individuals at risk of developing metabolic disorders. However, the limitation of this study arises from its small sample size, which restricts the generalizability of the findings. But, these findings hold significant implications for clinical practice, public health, and further research in metabolic disorders.

CONCLUSION

The TyG index, HGI, and IR demonstrated a significant association within the analyzed sample. These findings reinforce the high reliability of both indices in assessing IR and glucose metabolism, suggesting their potential as independent risk markers not influenced by FPG levels and other variables evaluated in this study.

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