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Original Article

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Association of insulin resistance in patients with type 1 diabetes mellitus with nutritional status, glycemic and lipid profile

Associação da resistência à insulina em pacientes portadores de diabetes mellitus tipo 1 com o estado nutricional, perfil glicêmico e lipídico

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Abstract

Introduction: Insulin resistance, although little investigated in individuals with type 1 diabetes mellitus, may be frequent in this population. Thus, accessible parameters to clinical practice are necessary to facilitate the screening of this condition. **Objective:** To evaluate the presence of insulin resistance in patients with type 1 diabetes mellitus using the triglyceride / glucose index and associate it with nutritional status, glycemic and lipid profile. **Methods:** Original cross-sectional study carried out with 45 adult patients (≥19 years old) treated at the Endocrinology and Diabetes outpatient clinic of a University Hospital in Fortaleza, Ceará, Brazil. Sociodemographic, anthropometric (weight and height), biochemical and clinical data (comorbidities and pharmacological treatment) were obtained from the medical records. The cutoff points proposed for the Mexican population were used to classify the triglyceride / glucose index, considering altered, values ≥ 4.55 for women and ≥ 4.68 for men. The normality of the quantitative variables was assessed using the Shapiro Wilk test and, to investigate associations, the Student t test and the Mann-Whitney test were used. A significance level of 5% was adopted for all tests used. **Results:** It was observed that 62.2% of the individuals showed altered levels of the triglycerides/glucose index. Individuals who had altered levels revealed higher values of fasting blood glucose, glycated hemoglobin, triglycerides, total cholesterol and LDL-c ($p < 0.05$). However, there was no significant association with HDL-c ($p = 0.22$), LDL-c ($p=0.07$), glycated hemoglobina ($p=0.057$) and Body Mass Index ($p = 0.33$). **Conclusions:** The triglyceride / glucose index as significantly associated with fasting glycemia, triglycerides and total cholesterol.

Keywords: endocrine system diseases; blood glucose; lipid metabolism disorders; body mass index.

Resumo

Introdução: A resistência à insulina, apesar de pouco investigada em indivíduos com Diabetes *mellitus* tipo 1, pode ser frequente nesse público. Assim, parâmetros acessíveis à prática clínica

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são necessários para facilitar o rastreio dessa condição. **Objetivo:** Avaliar a presença de resistência à insulina em pacientes com diabetes mellitus tipo 1 por meio do índice triglicerídeos/glicose e associar com estado nutricional, perfil glicêmico e lipídico. **Métodos:** Estudo original transversal realizado com 45 pacientes adultos (≥19 anos) atendidos no ambulatório de Endocrinologia e Diabetes de um Hospital Universitário de Fortaleza-CE. Obtiveram-se, a partir dos prontuários, dados sociodemográficos, antropométricos (peso e altura), bioquímicos e clínicos (comorbidades e tratamento farmacológico) dos pacientes. Utilizou-se os pontos de corte propostos para a população mexicana para classificação do índice triglicerídeos/glicose, considerando-se alterado, valores ≥ 4,55 para mulheres e ≥ 4,68 para homens. A normalidade das variáveis quantitativas foi avaliada por meio do teste de Shapiro Wilk e, para investigar associações utilizou-se o teste t de Student e o teste de Mann-Whitney. Adotou-se um nível de significância de 5% para todos os testes utilizados. **Resultados:** Observou-se que 62,22% dos indivíduos revelaram níveis alterados do índice triglicerídeos/glicose. Indivíduos que apresentaram níveis alterados revelaram valores mais elevados de glicemia de jejum, triglicerídeos e colesterol total (p<0,05). Entretanto, não se observou associação significativa com HDL-colesterol (p=0,22), LDL-colesterol (p=0,07), hemoglobina glicada (p=0,057) nem com IMC (p=0,33). **Conclusões:** O índice triglicerídeos/glicose associou-se significativamente com glicemia de jejum, triglicerídeos e colesterol total.

Palavras-chave: doenças do sistema endócrino; glicemia; distúrbios do metabolismo dos lipídeos; índice de massa corporal.

Introduction

Insulin resistance (IR) is defined as a condition in which insulin does not effectively perform its function, despite its preserved endogenous secretion or exogenous replacement. Thus, amounts of insulin greater than those considered normal are needed to exert its effect. IR can be influenced by ethnicity, puberty, pregnancy, aging and comorbidities, such as hypertension, type 2 diabetes mellitus (DM2), obesity and dyslipidemia, autoimmune diseases, infections and use of medications such as steroids[1,2].

In Type 1 Diabetes mellitus (DM1), an autoimmune disease characterized by the destruction of pancreatic β-cells and absence of insulin production, little attention is paid to the occurrence of IR when compared to DM2. However, studies have revealed that, with the progression of the disease, these individuals may have this condition. Despite this, the pathophysiological explanations for this association have not been fully elucidated[3].

The genesis of IR in DM1 is multifactorial and involves genetic, environmental and lifestyle factors. A family history of DM2 in patients with DM1 may represent a greater risk for the development of characteristic features of DM2, such as IR. Additionally, aspects related to lifestyle, such as sedentary lifestyle and poor eating habits, can contribute to the development of overweight and obesity, worse glycemic control and increased need for exogenous insulin doses, factors that can trigger or worsen IR[4].

The gold standard method for assessing insulin sensitivity is the hyperinsulinemic euglycemic clamp method. However, it is a costly, invasive method that is not applicable to clinical practice[5]. Thus, the glucose triglyceride index (TyG), which is equivalent to the product between blood glucose and serum levels of triglycerides in the same blood sample, represents an alternative to assess IR in a faster, more simplified and less expensive way, since triglyceride and fasting blood glucose are routinely used parameters[2]. In addition, TyG was found to better predict IR than Homeostasis Model Assessment (HOMA-IR) when compared to the hyperinsulinemic euglycemic clamp, and was significantly correlated with adiposity, metabolic parameters and subclinical atherosclerosis markers in

individuals with DM2 and with normal glucose tolerance[5].

In this context, considering the need for more accessible methods to assess IR in clinical practice and the scarcity of studies investigating the presence of this condition in adult patients with DM1, the present study aimed to assess the presence of IR in this public through the TyG index and associate with nutritional status, glycemic and lipid profile..

Materials and methods

Sample and type of study

This is a cross-sectional, retrospective study with an analytical component and a quantitative approach, carried out with adult patients diagnosed with DM1 treated at the Endocrinology and Diabetes outpatient clinic of a University Hospital, located in the city of Fortaleza, Ceará, Brazil.

The planning and execution of this study complied with the ethical principles recommended by Resolution 466 of the National Health Council of 20126, having been submitted and approved by the Research Ethics Committee of the hospital in question under CAAE No. 21760719.5.0000.5045.

Research design

The sample selection included patients seen from 2018 to 2020, and data collection took place between August and October 2020. The data used were collected from medical records and previously prepared nutritional care forms.

Inclusion and Exclusion Criteria

Patients of both sexes and aged 19 years or older were included, as the intention was to obtain an overview of TyG, not specifying by sex, and that the investigation of IR is more consistent in adults and with more time of disease (DM1). Exclusion criteria were defined as: pregnant women, patients with impaired renal and/or liver function, or who were undergoing cancer treatment, conditions that could have an impact on the metabolic state of individuals and interfere with the results of blood glucose and serum triglycerides, parameters used to calculate TyG.

Procedures

Anthropometric data of weight (kg) and height (m) of patients were collected to assess nutritional status using the Body Mass Index (BMI: weight (kg)/height (m)²) according to the World Health Organization (WHO) classification [7] for adults and with the recommendation of the Food and Nutritional Surveillance System/Ministry of Health[8] for the elderly (≥60 years old). Regarding sociodemographic and lifestyle data, information was obtained on gender, age, marital status, education, income, alcohol consumption, smoking and physical activity. Patient clinical data such as associated comorbidities, pharmacological treatment and biochemical data were also collected.

The calculation of the TyG index was calculated using the following formula: [Ln (fasting triglycerides (mg/dL) x fasting glucose (mg/dL)]/2, and the cutoff points proposed for the Mexican adult population were used, with values of 4.55 for women and 4.68 for men.[9] Since there are no defined cutoff points for the Brazilian population, therefore, changed TyG was considered to be the following values: ≥ 4.55 for women and ≥ 4.68 for men.

The data obtained were entered into the Microsoft Office Excel® program and then the JAMOVI® statistical program and the R® Software were used to perform their statistical analysis. Descriptive analysis of the study variables was performed, with categorical variables presented as simple frequencies and percentages, and numerical variables as mean (standard deviation) or median (interquartile range). To assess the normality of quantitative variables, the Shapiro Wilk test was used, and to investigate associations, the Student t test and the Mann-Whitney test were used. A significance level of 5% was adopted for all tests used.

Results

The sample consisted of 45 patients with DM1, predominantly female (n=30; 66.67%), with a median age of 37 (19-75) years, income of up to 3 minimum wages (n=29 ; 64.44%) having completed high school (n=29; 64.44%) and without a partner (n=14; 31.11%). In addition, 86.67% (n=39) of the sample denied alcohol consumption and 97.78% (n=44) denied smoking. The median BMI was 24kg/m^2 (16.9-36.4) and 53.33% (n=24) of the individuals were not overweight, despite the majority denying the practice of physical exercise (n=30; 66.67%) (Table 1).

Table 1. Nutritional, sociodemographic and lifestyle profile of patients with DM1. Fortaleza, Ceará, Brazil 2020

Variables	N	%
Gender		
Male	15	33.33
Female	30	66.67
Income		
≤ 3 minimum wages	29	64.44
>3 minimum wages	6	13.33
No information	10	22.23
Education		
< Complete high school	8	17.78
≥ Complete high school	29	64.44
No information	8	17.78
Marital status		
With partner	7	15.56
No partner	14	31.11
No information	24	53.33
Alcoholism		
Yes	6	13.33
No	39	86.67
Smoking		
Smoker	1	2.22
Non smoker	44	97.78
Physical activity		
Yes	15	33.33
No	30	66.67
Nutritional status *		
Overweight	19	42.22
Not overweight	24	53.33
No information	2	4.45
Total	**45**	**100**

Subtitle: * Overweight in adults (BMI ≥25kg/m^2); overweight in the elderly (BMI ≥27 kg/m^2).
Source: Prepared by the authors.

Regarding comorbidities, the most reported was dyslipidemia (n=10; 22.22%), followed by systemic arterial hypertension (n=6;13.34%) and hypothyroidism (n=5; 11.11%). As for the pharmacological treatment, the majority (n=32; 71.11%) made use of analogous insulins, but only 31.11% (n=14) performed carbohydrate counting. Furthermore, among oral medications, the most cited were statins (n=12; 26.67%) (Table 2).

Table 2. Clinical profile of patients with DM1 – comorbidities, pharmacological and nutritional treatment. Fortaleza, Ceará, Brazil 2020.

Variables	N	%
Systemic Arterial Hypertension		
Yes	6	13.34
No	39	86.66
Dyslipidemia		
Yes	10	22.22
No	35	77.78
Cardiovascular disease		
Yes	3	6.67
No	42	93.33
Hyperthyroidism		
Yes	1	2.22
No	44	97.78
Hypothyroidism		
Yes	5	11.11
No	40	88.89
Oral antidiabetics		
Yes	8	17.78
No	37	82.22
Type of insulin		
Human	2	4.44
Analogues	32	71.11
No information	11	24.45
Statin		
Yes	12	26.67
No	33	73.33
Antihypertensive		
Yes	8	17.78
No	37	82.22
CHO count		
Yes	14	31.11
No	20	44.44
No information	11	24.45
Total	**45**	**100**

Caption: CHO: carbohydrate.
Source: Prepared by the authors.

It was observed that 62.22% (n=28) of the individuals showed altered levels of TyG. The mean was 172mg/dL (± 81.3) and 115 mg/dL (±126) for fasting glucose and fasting triglyceridemia, respectively (Table 3).

Table 3. TyG index of patients with DM1. Fortaleza, Ceará, Brazil, 2020.

Variables	N	%
TyG		
Normal	17	37.78
Changed	28	62.22
Total	**45**	**100**

Caption: TyG: glucose triglyceride index; TyG changed to the following values: ≥ 4.55 for women and ≥ 4.68 for men.

Source: Prepared by the authors.

Regarding the glycemic and lipid profiles, respectively, individuals with altered levels of TyG showed higher values of fasting glucose (FG), triglycerides (TG) and total cholesterol (TC) (p<0.05). However, there was no significant association with HDL-c (HDL-cholesterol) (p=0.22), LDL-c (LDL-cholesterol) (p=0.07), HbA1c (glycated hemoglobin) (p=0.057) nor with BMI (p=0.33) (Table 4).

Table 4. Glycemic and lipid profile and BMI of patients with DM1 in relation to the TyG index. Fortaleza, 2020.

Variables	TyG changed		Normal TyG		p
	N	Average (SD)	N	Average (SD)	
fasting blood glucose (mg/dL)	28	216.6 (63.7)	17	98.4 (45.9)	**<0.01***
£ Glycated hemoglobin (%)	22	8.1 (1.3)	14	10.9 (5.0)	0.057*
Triglyceride (mg/dL)	28	148.9 (151.0)	17	59.3 (17.8)	**<0.01***
£ Total cholesterol (mg/dL)	26	187.2(43.2)	17	157.4 (39.8)	**0.02¥**
£LDL-c (mg/dL)	21	105 (30.0)	14	84.9 (33.9)	0.07¥
£HDL-c (mg/dL)	25	51.3(15.9)	14	57.8(15.7)	0.22¥
£IMC (kg/m²)	26	26.0 (5.4)	17	23.8 (3.0)	0.33*

Legend: p significant when <0.05; SD: standard deviation; LDL-c: LDL-cholesterol; HDL-c: HDL-cholesterol; BMI: body mass index; ¥: Student's t test; *: Mann-Whitney test; £: n does not total 45 due to lack of information in the medical record.
Source: Prepared by the authors.

Discussion

The present study revealed the presence of altered levels of the TyG index in 62.22% (n=28) of individuals with DM1, and this revealed a significant association with GJ, TG and TC. However, the TyG index was not significantly associated with HDL-c, LDL-c, HbA1c, nor with BMI.

It is believed that the development of IR in individuals with DM1 may be influenced by lifestyle factors, family history of DM2, genetic alterations, and even hyperinsulinization derived from the treatment with exogenous insulin[3]. However, chronic hyperglycemia is also an important contributor to IR, and insulin treatment has been shown to optimize glycemic control and minimize IR[10]. In addition, adiposity, resulting from physical inactivity, a diet rich in sugar and other rapidly absorbed carbohydrates, is considered one of the main triggering factors for IR. In this sense, adiposity may require higher doses of insulin by reducing its sensitivity, while higher doses of insulin favor weight gain, which motivates the development or worsens IR[3].

Not only excess weight, but especially the distribution of body fat plays a central role in the development of IR. Fat mainly concentrated in the visceral region is more inflammatory, that is, it has a greater capacity to secrete pro-inflammatory cytokines, such as TNF-α and IL-6, which participate in the genesis of IR by negatively interfering with the activation of the insulin receptor. Furthermore, visceral fat is more susceptible to lipolysis, thus increasing the levels of free fatty acids and their influx into the liver and skeletal muscle, thus favoring IR in these organs due to lipotoxicity[11].

In this context, hepatic IR causes an increase in gluconeogenesis by the liver, leading to hyperglycemia and contributing to the excessive production of very low density lipoprotein (VLDL), consequently increasing the serum levels of TG[11]. Although the present study did not assess the patients' fat distribution, this may explain the fact that most patients had altered levels of the TyG index despite a median BMI of 24.4 kg/m² and the absence of a significant association between altered TyG and BMI. That is, although classified as eutrophic, there is a possibility that these

individuals had a high concentration of abdominal fat regardless of the BMI, thus contributing to the results obtained. In an epidemiological study with individuals with DM1, the mean BMI was 25.27 kg/m^2, in which 30.9% were overweight and 13.5% were obese12. While in the DCCT study (Diabetes Control and Complications Trial) the mean BMI was 23.5 kg/m^2 [13]. A study with healthy young adults, with a mean BMI of 24.2 kg/m^2, identified IR through TyG in 9.8% of men and 17.4% of women[9]. No study using TyG as a marker for IR in subjects with DM1 was detected in the literature.

In addition to excess weight and visceral fat concentration, dietary pattern, an aspect not evaluated in the present study, also exerts an important influence on the pathophysiology of IR and metabolic syndrome (MS). Dietary pattern based on the consumption of sugary drinks and diet soft drinks, white breads, hamburgers and french fries was associated with IR and increased risk of DM2 in a study with more than 7,000 adult participants in England[14]. A three-year longitudinal follow-up study with Iranian adults revealed a significant reduction in the risk of IR in those who followed a plant-based, low-fat dietary pattern[15]. Regarding the lipid profile, the adoption of the Mediterranean dietary pattern in adult and elderly patients at high cardiovascular risk minimized the atherogenicity of LDL-c particles and improved the functionality of HDL-c particles in individuals with and without diabetes[16]. However, studies addressing the impact of dietary patterns on IR and other components of the metabolic syndrome in patients with DM1 are scarce in the literature.

Dyslipidemia manifested in patients with diabetes is often characterized by hypertriglyceridemia, high levels of LDL-c and reduced levels of HDL-c, conditions that encourage the development of cardiovascular disease, which is the main cause of mortality in patients with DM1. In this context, IR was able to predict coronary artery disease outcomes in patients with DM1[17]. A study with Brazilians, including individuals with DM2 and normal glucose tolerance, revealed a significant correlation between the TyG index and the distribution of fat deposits, metabolic parameters, including TC, LDL-c, HDL-c, fasting insulin, and markers of subclinical atherosclerosis related to IR[5].

A study carried out with non-diabetic individuals demonstrated that the TyG index, in comparison with other markers, presented a superior correlation with biochemical parameters associated with atherogenic dyslipidemia and with HbA1c[4]. A study carried out in the region of Navarra in Spain, with 5,014 patients without DM1 showed that higher levels of TyG were not associated with important cardiovascular risk factors, such as HDL-C and LDL-C, gender, age, smoking, hypertension and BMI. However, regardless of these, TyG was associated with an increased risk of cardiovascular disease, proving to be a powerful predictor of coronary artery disease[18], confirming the usefulness of the index in identifying individuals at high risk for a poor cardiovascular outcome.

The term double diabetes, which has been described since 1991, refers to the condition where there is manifestation of characteristics related to DM1 and DM2, that is, there is a combination of autoimmunity, insulin deficiency and IR. In this sense, it is highlighted that absolute insulin deficiency and IR are independent phenomena and that the latter can occur in individuals with or without diabetes[19]. In addition, a meta-analysis that evaluated IR in DM1 patients using the hyperinsulinemic euglycemic clamp revealed that IR is an important manifestation in DM1 patients, involving liver, peripheral and adipose tissue, and that it is present in both well and poorly controlled subjects[1]. A study with more than 31,000 adult patients with DM1 identified that 25.4% of them also met the diagnostic criteria for metabolic syndrome, proposed by the National Cholesterol

Education Program, which considers waist circumference and TG, HDL-c and GJ blood pressure levels. Additionally, it was shown that patients with DM1 and MS, called by the author as double diabetes, had a significantly higher prevalence of macrovascular complications and an increased risk of microvascular complications (nephropathy and retinopathy) when compared to individuals with DM1 without MS[12].

In this scenario, the possibility arises of IR being one of the factors responsible for the poor glycemic control of patients with DM1, despite the numerous advances in insulin treatment and glycemic monitoring technologies[20]. Meta-analysis involving more than 1,500 DM1 patients revealed that combined treatment of insulin with metformin for 3 months was able to reduce fasting and postprandial glucose levels, HbA1c and daily insulin dosage. In addition to demonstrating benefits on the lipid profile, minimizing the levels of TC, LDL-c and non-HDL cholesterol.[17].

Among the limitations of the study, the cross-sectional design itself stands out, which makes it impossible to analyze the cause and effect between the variables. In addition, considering that one of the objectives of the study was to assess the association of nutritional status with the TyG index, the use of parameters other than BMI would be convenient, since the classification of nutritional status defined only through this index becomes a failure and superficial, since it does not assess body composition. The absence of other parameters to assess the nutritional status and the failure to obtain some sociodemographic and biochemical data is justified by the fact that the research was carried out from secondary data and during the COVID-19 pandemic, which made it difficult to obtain certain information, thus setting up another limitation.

However, the present study becomes relevant as it aimed to investigate and was able to identify altered levels of the TyG index, a parameter used to identify IR, in adult patients with DM1. In addition, a significant association of the index with important glycemic (GJ) and lipid (TC and TG) parameters was revealed. In this sense, the study alerts to the possibility of the presence and possible need for treatment of IR for better metabolic control and prevention of micro and macrovascular complications in these individuals. Thus, considering the lack of studies that investigate the presence of IR in the context of DM1, especially using this index, the study becomes relevant to the scientific literature. In addition, the study suggests the possibility of using a more accessible IR marker for clinical practice, as it is based on commonly used biochemical parameters.

Conclusion

The TyG index was significantly associated with GJ, TG and CT in a group of adult patients with DM1. Individuals who had altered levels of TyG showed higher values of the parameters mentioned above.

Additional studies are needed to assess the potential use of TyG as a marker to estimate the presence of IR in patients with DM1, and to identify which factors are associated with its occurrence. Thus, the treatment would be more targeted and would help in better glycemic and metabolic management, thus minimizing the risk of complications and mortality in this population.

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