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Triglyceride-glucose index levels in patients with congenital hypogonadotropic hypogonadism and the relationship with endothelial dysfunction and insulin resistance

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Abstract

Introduction: The risk of cardiometabolic diseases is increased in patients with hypogonadism. The triglyceride-glucose (TyG) index is a novel surrogate marker of insulin resistance and is associated with cardiovascular diseases. We investigated the TyG index levels and the relationship with endothelial dysfunction and insulin resistance in patients with congenital hypogonadotropic hypogonadism (CHH).
Material and methods: A total of 98 patients with CHH (mean age 21.66 ± 1.99 years) and 98 healthy control subjects (mean age 21.69 ± 1.21 years) were enrolled. The demographic parameters, TyG index, asymmetric dimethylarginine (ADMA), high-sensitivity C-reactive protein (hs-CRP), and homeostatic model assessment of insulin resistance (HOMA-IR) levels were measured for all participants.
Results: The patients had higher waist circumference ($p < 0.001$), triglycerides ($p = 0.001$), insulin ($p = 0.003$), HOMA-IR ($p = 0.002$), ADMA ($p < 0.001$), and TyG index ($p < 0.001$) levels and lower HDL-C ($p = 0.044$) and total testosterone ($p < 0.001$) levels compared to healthy control subjects. TyG index levels significantly correlated with the ADMA ($r = 0.31$, $p = 0.003$) and HOMA-IR ($r = 0.32$, $p < 0.001$) levels. TyG index was also determinant of HOMA-IR levels ($ß = 0.20$, $p = 0.018$).
Conclusion: The results of the present study show that patients with CHH had increased TyG index levels. Also, the TyG index is independently associated with insulin resistance in patients with CHH. Long-term follow-up studies are warranted to find out the role of the TyG index in determining cardiometabolic risk in patients with hypogonadism. **(Endokrynol Pol 2021; 72 (3): 232–237)**

Key words: *triglyceride-glucose index; hypogonadism; ADMA; insulin resistance; congenital hypogonadotropic hypogonadism; cardiovascular risk*

Introduction

Besides the fertility disturbance, patients with hypogonadism have an increased risk of cardiometabolic diseases such as type 2 diabetes, hypertension, dyslipidaemia, or obesity [1–4]. This increased cardiometabolic risk is present even in young ages in patients with congenital hypogonadotropic hypogonadism (CHH) [1]. Although the exact mechanism of increased cardiometabolic disease risk is not fully elucidated, endothelial dysfunction, inflammation, and insulin resistance have been reported as the main pathophysiological pathways of this increased risk in patients with hypogonadism [3, 5, 6].

The triglyceride-glucose (TyG) index, which is calculated using fasting glucose and triglyceride levels, has recently been reported as a novel surrogate marker of insulin resistance [7–9]. The TyG index has been reported to show good correlation with hyperinsulinaemic euglycaemic clamp test and homeostasis model assessment for insulin resistance (HOMA-IR) [8, 10]. Recent studies also reported that increased TyG index levels are strongly associated with cardiometabolic diseases such as type 2 diabetes [11], hypertension [12], nonalcoholic fatty liver disease [13], and cardiovascular diseases [14].

The TyG index may also be associated with increased cardiometabolic risk in hypogonadism patients. However, there are very limited data about the TyG index levels in patients with hypogonadism. Also, there are no data about the relationship between TyG levels and endothelial dysfunction and insulin resistance in patients with CHH. Therefore, we designed this study to search for the answers to the following questions: 1 — Is there any difference between patients with CHH and healthy controls in terms of TyG index levels? 2 — Is there any association between TyG index and surrogate markers of endothelial dysfunction, insulin resistance, and inflammation in treatment-naïve patients with CHH?

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Material and methods

Study design and population

This cross-sectional study was performed by evaluating the hypogonadism database of the department of Endocrinology and Metabolism of a tertiary centre. The study group consisted of male subjects with CHH (n = 98, mean age 21.66 ± 1.99 years), and age- and body mass index (BMI)-matched male healthy volunteers (n = 98, mean age 21.69 ± 1.21 years). Patients who were previously given testosterone or human chorionic gonadotropin (hCG) therapy and with any chronic diseases or organ dysfunction were excluded. None of the control subjects had a chronic disorder or used any medications, including over-the-counter drugs. All subjects gave informed consent, and the Local Ethical Committee of Gulhane School of Medicine approved the study. A portion of the data for this study population was previously published [1, 15].

Detailed medical histories of all patients and control subjects were obtained before the study. The height, weight, and waist circumference of the patients and control subjects were measured with them wearing just their underwear. The BMI was computed as the ratio of weight to the square of height (kg/m^2). Waist circumference was measured on the line between the iliac crest and the lower costal margin parallel to the ground after subjects exhaled. Pubertal development of the patients was evaluated according to the Tanner stages. The diagnosis of CHH was based on a failure to undergo spontaneous puberty before 18 years of age and was confirmed by low serum total testosterone levels and normal or low gonadotropin levels. Pituitary hormones were evaluated in all patients to exclude panhypopituitarism. Pituitary or hypothalamic mass lesions were excluded by magnetic resonance imaging.

Sample collection and laboratory measurements

Venous blood samples were drawn from patients and control subjects between 08:00 and 09:00 h after overnight fasting for biochemical analyses. The samples were centrifuged for 15 min at 4000 g, aliquoted, and immediately frozen at −80°C for analyses. Fasting plasma glucose, total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) levels were measured by the enzymatic colorimetric method with an Olympus AU2700 auto analyser using reagents from Olympus Diagnostics (GmbH, Hamburg, Germany). Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula [16]. The serum basal insulin level, total testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) were measured by the chemiluminescence method with a Unice IDXI 800 Access Immunoassay System (Miami, FL, ABD). Insulin sensitivity was calculated by using the homeostatic model assessment-insulin resistance (HOMA-IR) by the following formula:

$$HOMA\text{-}IR = (insulin \times glucose)/405.$$

TyG index is the logarithm (Ln) of *(fasting blood glucose (mg/ dL) × TG(mg/dL)/2)* [10]. Plasma asymmetric dimethylarginine (ADMA) levels were measured by ELISA (Immundiagnostik, Bensheim, Germany). The minimum detectable concentration for ADMA was 0.05 μmol/L. High-sensitivity C-reactive protein (hs-CRP) levels were determined in serum by immunoturbidimetric fixed rate method using an Olympus AU-2700 autoanalyzer (Hamburg, Germany). Intraassay coefficient of variation (CV) and interassay CV were 5.8% and 3.1%, respectively. The minimum detectable concentration for hs-CRP was 0.07 mg/L.

Statistical analyses

All data were recorded on a computer database and analysed using SPSS 15.0 package program (SPSS, Inc., Chicago, IL, USA). Results were expressed as mean ± S.D. The variables were assessed for normality using Kolmogorov-Smirnov test, and Levene's test was used to evaluate the equality of variance. Intragroup changes at two time points were analysed by paired samples t-test or Wilcoxon signed-rank test, as appropriate. Inter-group differences were analysed by Student's t-test and Mann-Whitney U test as appropriate. Relationships between ADMA and HOMA-IR levels and clinical and biochemical parameters were evaluated by Pearson correlation coefficients. Differences were considered significant at $p < 0.05$.

Results

The demographic and biochemical characteristics of the patients and the control subjects are given in Table 1. A total of 98 patients with CHH and 98 healthy control subjects were included. The two groups were similar with regard to age and BMI. Waist circumference ($p < 0.001$), triglycerides ($p = 0.001$), insulin ($p = 0.003$), HOMA-IR ($p = 0.002$), ADMA ($p < 0.001$), and TyG index ($p < 0.001$) levels were significantly higher and HDL-C ($p = 0.044$) and total testosterone ($p < 0.001$) levels significantly lower in patients with CHH, compared to healthy control subjects.

To define whether ADMA and HOMA-IR levels were associated with demographic and clinical parameters, basic biochemical results, or TyG index, we performed a Pearson correlation analysis. There were negative correlations between plasma ADMA levels and BMI ($r = –0.24$, $p = 0.027$), HDL-C ($r = –0.25$, $p = 0.021$), total testosterone ($r = –0.70$, $p < 0.001$), FSH ($r = –0.49$, $p < 0.001$), and LH ($r = –0.59$, $p < 0.001$) and positive correlations between plasma ADMA levels and total-C ($r = 0.23$, $p = 0.041$), triglycerides ($r = 0.30$, $p = 0.004$), LDL-C ($r = 0.24$, $p = 0.028$), and TyG index ($r = 0.31$, $p = 0.003$). HOMA-IR levels were correlated negatively with total testosterone ($r = –0.25$, $p = 0.002$), and they correlated positively with BMI ($r = 0.27$, $p = 0.001$), waist circumference ($r = 0.41$, $p < 0.001$), glucose ($r = 0.28$, $p = 0.001$), triglycerides ($r = 0.23$, $p = 0.006$), insulin ($r = 0.99$, $p < 0.001$), and Tyg index levels ($r = 0.32$, $p < 0.001$) (Tab. 2).

Multiple regression analysis was applied to test the independent link between ADMA and HOMA-IR levels and potential functional correlates of these outcome variables. The multivariate analysis has shown that total testosterone levels ($\beta = –0.71$, $p = 0.001$) were the only independent determinant of plasma ADMA levels, while waist circumference ($\beta = 0.26$, $p = 0.045$) and TyG index levels ($\beta = 0.20$, $p = 0.018$) were the determinants of the HOMA-IR levels (Tab. 3).

Discussion

The results of the present study show that patients with CHH have higher plasma ADMA, HOMA-IR, and TyG index levels than the healthy control subjects. Moreover, the TyG index is significantly correlated with plasma ADMA and HOMA-IR levels and is applicable as the independent predictor of HOMA-IR levels. These

Table 1. *Demographic and metabolic parameters of patients with congenital hypogonadotropic hypogonadism (CHH) and healthy controls*

	Healthy controls [n = 98]	Patients with CHH [n = 98]	p
Age [year]	21.69 ± 1.21	21.66 ± 1.99	0.897
BMI [kg/m^2]	23.00 ± 2.21	22.28 ± 3.40	0.082
WC [cm]	79.58 ± 6.50	84.80 ± 10.95	< 0.001
FBG [mg/dL]	83.89 ± 10.36	85.94 ± 7.27	0.110
Total-C [mg/dL]	153.20 ± 34.66	161.18 ± 26.88	0.083
TG [mg/dL]	81.03 ± 33.56	105.58 ± 60.21	0.001
LDL [mg/dL]	86.32 ± 30.09	92.09 ± 22.31	0.138
HDL [mg/dL]	51.19 ± 15.34	47.44 ± 10.02	0.044
FSH [mIU/mL]	3.69 ± 2.47	1.34 ± 4.74	0.001
LH [mIU/mL]	5.06 ± 1.84	0.82 ± 3.26	<0.001
T. Testosterone [ng/mL]	540.32 ± 120.52	29.66 ± 27.97	<0.001
Insulin [μU/mL]	7.20 ± 4.77	9.97 ± 5.94	0.003
HOMA-IR	1.49 ± 1.10	2.12 ± 1.31	0.002
hs-CRP [mg/L]	0.92 ± 1.29	1.18 ± 1.10	0.241
ADMA [μmol/L]	0.34 ± 0.06	0.66 ± 0.16	< 0.001
TyG index	8.04 ± 0.48	8.30 ± 0.49	< 0.001

BMI — body mass index; WC — waist circumference; FBG — fasting blood glucose; Total C — total cholesterol; TG — triglyceride; LDL — low-density lipoprotein cholesterol; HDL — high-density lipoprotein cholesterol; FSH — follicle stimulating hormone; LH — luteinizing hormone; T. Testosterone — serum total testosterone; HOMA-IR — homeostatic model assessment of insulin resistance; hs-CRP — high-sensitivity C-reactive protein; ADMA — asymmetric dimethylarginine; TyG Index — triglyceride–glucose index

Table 2. *Correlation analysis between asymmetric dimethylarginine (ADMA), homeostatic model assessment of insulin resistance (HOMA-IR), and clinical and biochemical parameters*

	ADMA		HOMA-IR	
	r	p	r	p
BMI [kg/m^2]	–0.235	0.027	0.267	0.001
WC [cm]	0.105	0.359	0.406	< 0.001
FBG [mg/dL]	0.101	0.349	0.278	0.001
Total-C. [mg/dL]	0.225	0.041	–0.023	0.785
Triglyceride [mg/dL]	0.299	0.004	0.225	0.006
HDL [mg/dL]	–0.245	0.021	–0.150	0.070
LDL [mg/dL]	0.244	0.028	–0.024	0.778
Insulin [μU/mL]	0.217	0.059	0.987	< 0.001
TyG Index	0.309	0.003	0.321	< 0.001
hsCRP [mg/L]	0.153	0.162	0.154	0.115
T. Testosterone [ng/mL]	–0.703	< 0.001	–0.253	0.002
FSH [mIU/mL]	–0.486	< 0.001	0.066	0.478
LH [mIU/mL]	–0.585	< 0.001	–0.030	0.744

BMI — body mass index; WC — waist circumference; FBG — fasting blood glucose; Total C. — total cholesterol; TG — triglyceride; LDL — low-density lipoprotein cholesterol; HDL — high-density lipoprotein cholesterol; FSH — follicle stimulating hormone; LH — luteinizing hormone; T. Testosterone — serum total testosterone; HOMA-IR — homeostatic model assessment of insulin resistance; hs-CRP — high-sensitivity C-reactive protein; ADMA — asymmetric dimethylarginine; TyG Index — triglyceride–glucose index

findings imply that the TyG index may be a useful and practical measure for assessing insulin resistance in patients with CHH. To our knowledge, the current study is the first to show the levels of the TyG index and its relationship with endothelial dysfunction and insulin resistance in patients with CHH.

Table 3. *Linear regression analysis using asymmetric dimethylarginine (ADMA) and homeostatic model assessment of insulin resistance (HOMA-IR) as the dependent variables*

Dependent Variable	Independent variables	B coefficient	t value	p
ADMA [μmol/L]	BMI [kg/m²]	–0.050	–0.451	0.654
	HDL [mg/dL]	0.011	0.101	0.920
	LDL [mg/dL]	0.118	1.111	0.271
	TyG Index	0.104	0.929	0.357
	T. Testosterone [ng/mL]	–0.707	–3.367	0.001
	FSH [mIU/mL]	–0.068	–0.334	0.740
	LH [mIU/mL]	0.208	0.903	0.370
HOMA-IR	BMI [kg/m²]	0.075	0.623	0.535
	WC [cm]	0.259	2.026	0.045
	TyG Index	0.197	2.402	0.018
	T. Testosterone [ng/mL]	0.133	–1.504	0.135

BMI — body mass index; WC — waist circumference; LDL — low-density lipoprotein cholesterol; HDL — high-density lipoprotein cholesterol; FSH — follicle stimulating hormone; LH — luteinizing hormone; T. Testosterone — serum total testosterone; HOMA-IR — homeostatic model assessment of insulin resistance; ADMA — asymmetric dimethylarginine; TyG Index — triglyceride–glucose index

It is well-known that patients with hypogonadism are at increased cardiometabolic risk [2, 17, 18]. Although the exact mechanism of increased cardiovascular risk of patients with hypogonadism is not clear, the classical pathways of atherosclerosis such as endothelial dysfunction, insulin resistance, and inflammation are thought to be involved [3, 19, 20]. Nitric oxide (NO), an endothelium derived mediator, is a potent endogenous vasodilator, and decreased levels of NO may cause endothelial dysfunction and increased risk of cardiovascular disease. ADMA, an endogenous inhibitor of nitric oxide synthase, is a well-known surrogate marker of endothelial dysfunction [21]. Also, the HOMA-IR level is a well-known surrogate marker of insulin resistance [22]. In the present study, the worse lipid profile, and higher waist circumference and insulin levels in patients with CHH indicate that these patients had metabolic derangements. Also, we showed again that patients with CHH have increased ADMA and HOMA-IR levels when compared with healthy subjects. These findings imply that patients with CHH have impaired endothelial functions and increased insulin resistance even at younger ages [15, 23]. However, these surrogate markers are generally used in scientific studies and are not practical to show the increased cardiometabolic risk of patients with hypogonadism in daily use.

The TyG index is a novel surrogate marker of insulin resistance, first proposed by Guerrero-Romero et al. in 2008 [7]. Previous studies reported that the TyG index correlates greatly with hyperinsulinaemic euglycaemic clamp test and HOMA-IR levels [7, 8, 10]. TyG index levels also increased in many cardiometabolic diseases such as coronary artery disease, hypertension, type 2 diabetes, obesity, and metabolic syndrome, all of which have increased prevalence in patients with hypogonadism [11, 14, 24]. In the present study, we showed that TyG index levels were higher in patients with CHH compared to the healthy subjects. To our knowledge, there are no data showing the TyG index levels in patients with CHH. However, there is a study that indicates the TyG index levels in patients with hypogonadism [25]. In this study, Zhang et al. found out that patients with hypogonadism had significantly higher TyG index levels compared with men without hypogonadism. However, the patients with hypogonadism in this study were elderly, and the aetiology of hypogonadism is not clear. Similarly, we showed higher TyG index levels in younger and treatment-naïve patients with CHH.

HOMA-IR levels have been used in many studies to detect insulin resistance. However, it is not a practical method for measuring insulin resistance on an individual basis, and it is used mostly in scientific studies. Previous studies reported that the TyG index could be used as a surrogate marker for insulin resistance instead of HOMA-IR [8]. In our study, we found that the TyG index correlated with both ADMA and HOMA-IR levels. Moreover, with waist circumference, the TyG index was the independent determinant of the HOMA-IR levels. Zhang et al. found out that the TyG index had better predictive power for hypogonadism than HOMA-IR [25]. We found that the TyG index also had predictive power for HOMA-IR levels even in younger and treatment-naïve patients with CHH. These findings imply that the TyG index may be used as a simple and practical measure to predict insulin resistance in patients with CHH. Additionally, increased TyG index

levels and its correlation with ADMA and HOMA-IR levels may mean that this index may be an indicator of increased cardiovascular risk in these patients.

There are several limitations and strengths of the present study. First of all, the cross-sectional design of the study may preclude further mechanistic comments. In addition, the study population, comprising young, treatment-naïve patients with CHH, may not be representative of the general population of patients with hypogonadism. Finally, the small sample size may be another limitation; however, treatment-naive adults with CHH are uncommon, and we think that the number of subjects in this study was adequate for evaluation. Despite these limitations, the presence of the homogeneous study population and the lack of confounding factors, such as chronic metabolic disorders and concomitant medications, are the strengths of the study.

Conclusions

The present study shows that patients with CHH have increased TyG index levels, which are significantly correlated with the surrogate markers of endothelial dysfunction and insulin resistance. Moreover, the TyG index has an independent predictive power for insulin resistance in treatment-naïve young patients with CHH. However, prospective long-term studies are warranted to find out the role of the TyG index in determining cardiometabolic risk in patients with hypogonadism.

Ethics approval and consent to participate

All subjects gave informed consent, and the Local Ethical Committee of Gulhane School of Medicine approved the study. A portion of the data for this study population was published previously [1,15].

Human and animal rights

No animals were used in this study. The research was performed in humans in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (http://www.wma.net/en/ 20activities/10ethics/10helsinki/).

Conflict of interest

No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counselling, expertise, working conditions, shareholding, and similar situations in any firm.

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