Triglyceride Response to Oral Glucose Load: Is it Exaggerated in Metabolic Syndrome?

Orçun Can[1], Mehmet Uzunlulu[1], Aytekin Oğuz[1], Aysun Semerci[1], Gökhan Gönenli[1], Özge Telci Çaklılı[1], Ferruh Kemal İsman[2], Banu İşbilen-Başok[2]

[1]Department of Internal Medicine, İstanbul Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey
[2]Department of Medical Biochemistry, İstanbul Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Objective: Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors related to insulin resistance. Data show that triglyceride (TG) levels following an oral glucose tolerance test (OGTT) are higher among obese and insulin-resistant cases associated with metabolic risk factors. In this study, we aimed to assess whether an exaggerated TG response was present in cases with MetS who had undergone OGTT.

Methods: In total, 88 cases (70 females, 18 males) without diabetes who were aged older than 18 years were recruited. All the cases underwent 75-gram OGTT. Fifty-one cases (42 females, 9 males; mean age: 48.69±10.13 years) with MetS according to the International Diabetes Foundation formed the MetS group, while 37 cases without MetS (28 females, 9 males; mean age: 48.78±9.18 years) formed the control group.

Results: OGTT 0-, 1-, and 2-hour TG levels were 170.96±81.10 mg/dL, 166.94±72.82 mg/dL, and 157.76±74.29 mg/dL in the MetS group and 116.46±47.60 mg/dL, 115.35±46.01 mg/dL, and 108.51±49.33 mg/dL in the control group, respectively. The 2-hour TG levels were significantly decreased in both groups compared with the 0- and 1-hour levels (p=0.001 for both). In both the groups, glucose and insulin levels significantly increased in the 1st hour compared with the 0th hour and significantly decreased in the 2nd hour compared with the 1st hour (p=0.001 for both).

Conclusion: In this study, the presence of MetS did not have an effect on TG response to OGTT. The decrease in TG levels in both groups may be associated with the acute decreasing effect of early-phase insulin on TG.

Keywords: Metabolic syndrome, insulin resistance, oral glucose tolerance test, triglyceride

INTRODUCTION

Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors characterized by abdominal obesity, high blood pressure, atherogenic dyslipidemia, hyperglycemia, and a prothrombotic and proinflammatory state, and it is an important risk factor for the development of atherosclerotic cardiovascular diseases and type-2 diabetes mellitus (DM) (1, 2). Dyslipidemia observed in MetS patients, also known as atherogenic dyslipidemia triad which is characterized by low high-density lipoprotein-cholesterol (HDL-C), high triglyceride (TG), and small dens low-density lipoprotein-cholesterol levels increases in these individuals and is believed to be associated with insulin resistance (3).

Increasing data demonstrate that both fasting and postprandial TG levels are associated with coronary artery diseases (4, 5). TG levels following an oral glucose tolerance test (OGTT) have been shown to be higher among cases with obesity and insulin resistance associated with metabolic risk factors (6). In this study, we tested the following hypothesis: TG response, in association with insulin resistance, is higher in MetS patients than in non-MetS patients following carbohydrate loading. To this end, the TG responses of patients with and without MetS following OGTT were compared and the relationship between their post-OGTT TG responses and metabolic risk factors were evaluated.

METHODS

A total of 88 cases (70 females, 18 males) without diabetes aged older than 18 years who were referred to Istanbul Medeniyet University Goztepe Training and Research Hospital Internal medicine Clinic and who were eligible according to the inclusion and exclusion criteria were recruited. Ethics Committee's approval (Date: 01.08.2013, Decision Number: 2013/0036) and written consent from the participants were obtained beforehand, and the Declaration of Helsinki principles were followed throughout the study.

Inclusion Criteria

Impaired fasting glucose levels (fasting glucose level between 100 and 125 mg/dL) or HbA1c levels between 5.7% and 6.4% were used as indicators for OGTT.

Exclusion Criteria

Patients with type-1 or type-2 diabetes or patients using anti-diabetes treatment, patients with chronic liver or renal di-

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Address for Correspondence: Banu İşbilen Başok,
E-mail: drisbilen@yahoo.com

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seases, heart failure, nephrotic syndrome, hypo- or hyperthyroidism, malabsorption disorders and/or enteropathies, use of medications that affect lipid and glucose metabolism, TG levels >400 mg/dL, and any condition that prevented measurement of the waist circumference (pregnancy, ascites or abdominal mass, etc.) were excluded from the study.

Study Design

Demographic characteristics, comorbidities, cigarette smoking habit, alcohol use, and antihypertensive drug use information were collected from the participants meeting the patient selection criteria, and their anthropometric and biochemical data were recorded. Cases diagnosed with MetS according to the International Diabetes Foundation's (IDF) definition were allocated to the MetS group and those without MetS formed the control group (7). Both groups were administered an OGTT with 75 grams of glucose. The groups were compared based on their demographic, anthropometric, and biochemical characteristics; their glucose, insulin, and TG levels; and changes at OGTT 0-, 1-, and 2-hour time points. Correlation analyses were performed to evaluate the relationship between post-OGTT TG concentrations and metabolic risk factors, such as waist circumference, body mass index (BMI), fasting plasma glucose, lipid parameters, blood pressure, insulin, and homeostasis model assessment-insulin resistance (HOMA-IR).

The protocol recommended by The World Health Organization was implemented for OGTT (8). OGTT 2-hour glucose values of <140 mg/dL were identified as normal glucose tolerance (NGT), 140–199 mg/dL as impaired glucose tolerance (IGT), and ≥200 mg/dL as DM (9).

Anthropometric Measurements

Blood pressure was measured with an appropriate mercury sphygmomanometer, based on Korotkoff phase I and phase V sounds, on both arms, in a sitting position, following a 10-minute rest at minimum. A 2nd measurement was made on the arm with the higher blood pressure, with at least 3-minute intervals between the two measurements, after which the mean of the systolic and diastolic blood pressures was recorded. Body weight, waist circumference, and height were measured via standard measurement tools by the same person. Waist circumference was measured with the patient standing and lightly exhaling, at the narrowest area of the waist across the plane crossing between spina iliaca anterior superior and arcus costa. BMI was calculated by dividing the patient's weight in kilograms by their height in meters squared (kg/m^2).

Biochemical Measurements

Following a 12-hour fasting, venous blood samples were collected for fasting glucose, insulin, HbA1c, total cholesterol (TC), HDL-C, non-HDL-C, TG, TG/HDL-C, and LDL-C measurements. OGTT was performed with 75 g of glucose and venous blood samples were collected for 0, 1 and 2-hour glucose, TG, and insulin measurements. These samples collected at the OGTT 0, 1, and 2-hour time points were drawn into gel tubes not containing anticoagulants and were centrifuged for 10 minutes at 2500 g within one hour. Glucose, TG, and insulin analyses in the serum samples were performed simultaneously. Glucose and TG measurements were made using the COBAS 8000 analyzer (Roche Diagnostics GmbH, Germany). Serum insulin levels were measured with the chemiluminescence method using an Access DxI 800 Access analyzer (Beckman Coulter Inc. USA). HOMA-IR, which involves the evaluation of the insulin resistance by using fasting glucose and fasting insulin concentrations, was used to assess insulin resistance and was simply calculated by the following formula: fasting plasma glucose×fasting insulin/22.5 (10).

Statistical Analysis

Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA) were used. In addition to the descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum), for the comparison of quantitative data across two groups, the Student's t-test was used for normally distributed variables and the Mann–Whitney U test was used for non-normally distributed parameters. A repeated measures test was performed for within-group comparisons of variables with normal distribution and the Bonferroni correction was used for the evaluation of dual comparisons. The Friedman test was used for within-group comparisons of non-normally distributed parameters, while a Wilcoxon signed rank test was used for the evaluation of dual comparisons. Pearson's chi-square test, a Fisher–Freeman–Halton exact test, and Yates' continuity correction test were used to compare qualitative data. The relationships between the parameters were evaluated with Pearson's and Spearman's correlation analyses. The level of significance was set as $p<0.01$ and $p<0.05$.

RESULTS

There were 88 non-diabetic cases (70 females, 18 males; mean age: 48.73±9.69 years) included in the study. The MetS group consisted of 51 cases (42 females, 9 males) diagnosed with MetS, while the remaining 37 non-MetS cases (28 females, 9 males) were included in the control group.

The clinical characteristics of the groups are displayed in Table 1. Age and gender distribution were similar across groups. The frequency of antihypertensive drug use ($p=0.001$), BMI ($p=0.001$), waist circumference ($p=0.001$), systolic blood pressure ($p=0.028$), TG ($p=0.001$), insulin ($p=0.009$), and HOMA-IR ($p=0.045$) were higher in the MetS group than in the control group, while HDL-C ($p=0.001$) was lower in the MetS group.

Post-OGTT NGT and IGT were observed in 72.7% (72.5% in the MetS group and 73% in the control group, $p>0.05$) and 27.3% (27.5% in the MetS group and 27% in the control group, $p>0.05$) of the cases, respectively.

The changes in glucose and insulin levels during OGTT are presented in Tables 2 and 3. In both the groups, glucose and insulin levels significantly increased in the 1st hour compared with the 0th hour and then significantly decreased in the 2nd hour compared with the 1st hour ($p=0.001$ for both). The changes in TG during OGTT are shown in Table 4. The OGTT 2-hour TG levels

Table 1. Clinical characteristics of the study groups

	Total (n=88)	MetS group (n=51)	Control group (n=37)	p
Age (years)	48.73±9.69	48.69±10.13	48.78±9.18	0.963
Gender (female/male) (n, %)	70(79.5)/18(20.5)	42(82.4)/9(17.6)	28(75.7)/9 (24.3)	0.618
Cigarettes (n, %)	20 (22.7)	12 (23.5)	8 (21.6)	0.923
Alcohol (n, %)	12 (13.6)	5 (9.8)	7 (18.9)	0.360
Antihypertensive drugs (n, %)	27 (30.7)	25 (49.0)	2 (5.4)	0.001
Body mass index (kg/m^2)	31.52±5.96	33.98±5.87	28.12±4.20	0.001
Waist circumference (cm)	95.53±11.63	100.31±11.23	88.95±8.66	0.001
Systolic blood pressure (mmHg)	120.23±15.92	123.24±17.49	116.08±12.54	0.028
Diastolic blood pressure (mmHg)	73.81±10.14	75.39±10.67	71.62±9.06	0.085
Fasting plasma glucose (mg/dL)	107.48±6.11	107.47±6.60	107.49±5.43	0.990
Total cholesterol (mg/dL)	217.53±47.10	214.65±37.75	221.51±57.90	0.531
Triglyceride (mg/dL)	148.05±73.82	170.96±81.10	116.46±47.60	0.001
HDL-cholesterol (mg/dL)	51.07±13.48	46.65±13.41	57.16±11.12	0.001
LDL-cholesterol (mg/dL)	135.20±41.93	132.16±34.52	139.41±50.62	0.454
Non-HDL-cholesterol (mg/dL)	165.22±44.98	167.80±37.13	161.65±54.34	0.554
Triglyceride/HDL-cholesterol	3.31±2.28	4.16±2.58	2.14±0.96	0.170
Insulin (μU/mL)	8.76±4.50	9.70±4.88	7.47±3.60	0.009
HOMA-IR	2.02±1.06	2.20±1.12	1.77±0.93	0.045

MetS: metabolic syndrome; HOMA-IR: Homeostasis Model of Assessment-Insulin Resistance, Data are expressed as mean±SD, unless indicated otherwise.

decreased significantly in both the groups compared with the 0-hour and 1-hour levels (p=0.001 for both).

In the MetS group, OGTT 2-hour TG levels were positively correlated with waist circumference (r=0.360, p=0.009), fasting plasma glucose (r=0.358, p=0.009), insulin (r=0.423, p=0.002), and HOMA-IR (r=0.432, p=0.002), while they were negatively correlated with HDL-C (r=−0.517, p=0.001).

DISCUSSION

The results of this study did not support the hypothesis that the TG response, in association with insulin resistance, may be excessive among MetS patients compared to non-MetS patients following carbohydrate loading, and in fact oppositely demonstrated that TG levels significantly decreased. On the other hand, the significant correlation observed between the post-OGTT TG levels of MetS patients and the MetS parameters supports the association between TG and insulin resistance.

While it is still a topic of debate whether hypertriglyceridemia is an independent risk factor for coronary artery disease, increasing evidence shows that postprandial hypertriglyceridemia contributes to the development of atherosclerosis and coronary artery diseases (11, 12). It is known that coronary artery disease patients have increased excessive postprandial lipemia and increased lipoprotein residue rich in TG (13). Mixed meals (including various ratios of carbohydrate, fat, and protein) or oral metabolic tests (standard fat solutions) are used in postprandial hypertriglyceridemia evaluation, and both methods demonstrate postprandial plasma triglyceride concentrations may peak about 4 hours after a mixed food meal in normal subjects, but the peak is delayed in subjects with hypertriglyceridemia (14–16). On the other hand, it has been demonstrated that obese individuals are more sensitive to hypertriglyceridemia induced by carbohydrates than normal-weight individuals following carbohydrate loading and that post-OGTT plasma TG levels are higher among obese and insulin-resistant cases and are associated with metabolic risk factors (6). Nevertheless, the TG response of MetS patients to OGTT remains unknown.

It is known that free fatty acids (FFAs) derived from serum TGs increase hepatic glucose production and induce hepatic insulin resistance; hence this may explain the robust association of TGs and FFAs with insulin resistance and glucose (16). In this study, the hypothesis was tested that the TG response, in association with insulin resistance, may be excessive among MetS patients compared to non-MetS patients following carbohydrate loading. The TG responses of cases with MetS and without MetS were compared. Our results showed that OGTT 2-hour TG levels significantly decreased in both groups, thus they did not support the hypothesis that TG response to carbohydrate loa-

Table 2. Glucose levels upon the oral glucose tolerance test

Glucose (mg/dL)		Total (n=88)	MetS group (n=51)	Control group (n=37)	p
0-hour		93.19±8.61	92.14±7.91	94.65±9.41	0.178
1-hour		170.28±42.19	175.65±42.91	162.89±40.59	0.163
2-hour		129.70±33.79	130.67±35.40	128.38±31.87	0.756
	p	**0.001**	**0.001**	**0.001**	
Change					
1- vs. 0-hour	Difference	77.09±40.16	83.51±39.68	68.24±39.66	0.059
	p	0.001	0.001	0.001	
2- vs. 0-hour	Difference	36.51±32.33	38.53±34.34	33.73±29.58	0.419
	p	0.001	0.001	0.001	
2- vs. 1-hour	Difference	−40.58±39.42	−44.98±41.94	−34.51±35.33	0.248
	p	0.001	0.001	0.001	

MetS: Metabolic syndrome. Data are expressed as mean±SD.

Table 3. Insulin levels upon the oral glucose tolerance test

Insulin (μU/mL)		Total (n=88)	MetS group (n=51)	Control group (n=37)	p
0-hour		8.76±4.50	9.70±4.88	7.47±3.60	0.009
1-hour		60.15±29.73	65.53±29.88	52.72±28.24	0.030
2-hour		49.70±31.03	52.69±33.47	45.59±27.21	0.342
	p	**0.001**	**0.001**	**0.001**	
Change					
1- vs. 0-hour	Difference	51.38±28.31	55.84±27.90	45.25±28.08	0.050
	p	0.001	0.001	0.001	
2- vs. 0-hour	Difference	40.94±29.23	42.99±31.11	38.12±26.59	0.449
	p	0.001	0.001	0.001	
2- vs. 1-hour	Difference	−10.44±29.23	−12.84±34.98	−7.13±18.60	0.444
	p	0.001	0.015	0.016	

MetS: Metabolic syndrome. Data are expressed as mean±SD.

ding may be excessive in MetS patients. The decrease in TG levels at OGTT hour 2 in this study was probably due to the acute reducing effect of early-phase insulin secretion in OGTT on TG, as it is known that early-phase insulin secretion may lead to increases in lipolysis inhibition and lipoprotein lipase activity (17). Therefore, the peak OGTT 1-hour insulin levels, in parallel with glucose levels and the significant decrease in 2-hour insulin levels, support this finding. In this study, we determined OGTT 2-hour TG levels to be significantly correlated to parameters associated with insulin resistance, such as fasting blood glucose, waist circumference, HDL-C, TG/HDL-C, insulin, and HOMA-IR, in patients with MetS. This finding supports the idea that TG levels are associated with insulin resistance among MetS patients (1).

Study Limitations

The selection of enrolled patients among the prediabetic cases in terms of OGTT indication may be a limitation. Having healthy control subjects could lead to a better interpretation of the results, but administering OGTT to a healthy group is not part of common practice. In addition, patients with NGT and IGT are evaluated together in our study and the combined interpretation of these two groups may constitute a limitation. However, the incidence of NGT and IGT patients in both the MetS and control groups was found to be similar, which may also nullify this limitation.

CONCLUSION

The results of the present study did not support the hypothesis that response may be excessive among MetS patients following

Table 4. Triglyceride levels upon the oral glucose tolerance test

Triglyceride (mg/dL)		Total (n=88)	MetS group (n=51)	Control group (n=37)	p
0-hour		148.05±73.82	170.96±81.10	116.46±47.60	0.001
1-hour		145.25±67.67	166.94±72.82	115.35±46.01	0.001
2-hour		137.06±69.12	157.76±74.29	108.51±49.33	0.001
	p	**0.001**	**0.001**	**0.001**	
Change					
1- vs 0-hour	Difference	−2.80±13.04	−4.02±15.21	−1.11±9.18	0.068
	p	0.142	0.195	1.000	
2- vs 0-hour	Difference	−10.99±18.30	−13.20±20.53	−7.95±14.42	0.379
	p	0.001	0.001	0.006	
2- vs 1-hour	Difference	−8.19±14.14	−9.18±16.28	−6.84±10.59	0.990
	p	0.001	0.001	0.001	

MetS: Metabolic syndrome, Data are expressed as mean±SD.

carbohydrate loading. It was observed that TG levels significantly decreased in association with early-phase insulin secretion in both MetS and non-MetS patients. On the other hand, the significant correlation of post-OGTT TG levels with HOMA-IR and MetS parameters supports the association between TG and insulin resistance.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Medeniyet University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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