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CARDIOMETABOLIC AND RENAL DYSFUNCTIONS IN TYPE-2 DIABETES MELLITUS**

## GENDER DIFFERENCES OF TRIGLYCERIDE GLYCEMIC INDEX AS A MARKER OF CARDIOMETABOLIC AND RENAL DYSFUNCTIONS IN TYPE-2 DIABETES MELLITUS

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### ABSTRACT

**Introduction:** Triglyceride glycemic index (TGI), a product of the serum triglyceride and fasting blood glucose, is a documented better marker of insulin resistance than the validated homeostasis model assessment (HOMA). A detailed understanding could minimize the pan-systemic inflammatory changes associated with its elevation. This study assessed the relationship between TGI and metabolic/cardiovascular dysfunctions in type 2 diabetes mellitus (T2DM).

**Methods:** This cross-sectional study analyzed the data of 192 T2DM patients to assess the TGI and determined its sociodemographic, clinical, and laboratory correlates.

**Results:** The mean age (which included 6.2% females) was 60.4±11.6 years. Central obesity, microalbuminuria and elevated TGI were more common in women,  $p=0.04$ ,  $p=0.04$  and  $p=0.32$  respectively. TGI was associated with aging ( $p=0.002$ ), hypertension ( $p<0.001$ ), hyperhomocysteinemia ( $p<0.001$ ), poor glycemic control ( $p=0.07$ ) and microalbuminuria ( $p=0.06$ ). The higher TGI in women (who had lower fasting glucose levels) reflects the disproportionately higher

hypertriglyceridemia in them compared to the men. Age-related TGI reflected the large proportion (56.2%) of post-menopausal women among the elderly population. The pan-systemic inflammatory effect of elevated TGI was highlighted by its positive relationship with LVH ( $p<0.001$ ), elevated fasting insulin ( $p=0.04$ ), and declining kidney function ( $p=0.33$ ). Predictors of elevated TGI were central obesity, hypertension, hyperhomocysteinemia, atherogenic index of plasma, cardiac risk ratio and left ventricular hypertrophy

**Conclusion:** Elevated TGI is common in T2DM and is associated with cardiometabolic and kidney function derangements. An optimized control of hyperhomocysteinemia and metabolic syndrome (MetS) in association with lifestyle modification is imperative in reducing the TGI and the dysfunctions associated with its elevation.

**Keywords:** Triglyceride glycemic index, central obesity, atherogenic index of plasma, cardiac risk ratio, left ventricular hypertrophy.

### INTRODUCTION

Hypertriglyceridemia and hyperglycemia have been associated with derangements in cardiometabolic and kidney function in type 2

diabetes mellitus (T2DM).<sup>1,2</sup> While specific consensus has not been reached despite continuing research in this field, it is worth noting that this proven association has led to various adjustments in the criteria for diagnosis and treatment.<sup>3</sup> This is geared towards formulating a healthy lifestyle encompassing an ideal weight, regular exercises, lower dietary fat intake and treatment of metabolic syndrome (MetS), aimed at lowering the morbidity and mortality rates associated with cardiometabolic dysfunction.<sup>1-3</sup> In diabetics, chronic hyperglycemia-induced formation of advanced glycosylated end-products (AGEs) and hyalinosis have been associated with deranged lipids, particularly hypertriglyceridemia.<sup>4</sup> This has subsequently generated much interest in the triglyceride glycemic index (TGI) as an important cardiometabolic measure that could be useful in the cardiometabolic risk stratification.<sup>1,5</sup> In addition, TGI has been documented to be useful in assessing insulin resistance.<sup>6</sup>

Over the past 3-4 decades, the National Cholesterol Education Program Adult Treatment Plan IV {(NCEP) ATP IV}, the National Institutes of Health and various international, regional and national bodies have had conferences, at times reaching consensus, to evaluate the role of hypertriglyceridemia in cardiovascular risk assessment aimed at outlining recommendations that would guide diagnosis and treatment of dyslipidaemia.<sup>2,3,6-8</sup> Similarly, the International Diabetic Federation (IDF), the American Diabetes Association (ADA) and the World Health Organization (WHO) have pivoted various measures aimed at formulating diagnostic and treatment guidelines for the optimal management of diabetes.<sup>9-10</sup> The rising prevalence of obesity, diabetes, insulin resistance and dyslipidemia has led to the progressive reductions in diagnostic and treatment thresholds.<sup>8-10</sup> A multiracial and multiethnic study conducted in the United States reported a progressive increase in the prevalence of hypertriglyceridemia, with reductions in the levels of low density lipoproteins cholesterol (LDL-C), suggesting

a leading hypertriglyceridemia role in the etiology of the dyslipidemia-associated cardiometabolic and renal dysfunction.<sup>12</sup>

The American Heart Association (AHA) in reaffirming the contribution of triglyceride-rich lipoproteins (chylomicrons, very low-density lipoprotein (VLDL) and LDL-C) in the pathophysiologic mechanisms of atherogenicity, emphasized the need to prevent hypertriglyceridemia, in their report on dietary sugar intake, childhood and adolescent obesity.<sup>13</sup> The AHA recommended lifestyle changes to minimize hypertriglyceridemia and improve overall cardiometabolic health.<sup>13</sup> Though the synergy of risk factors for hypertriglyceridemia-associated cardiometabolic disease in T2DM is augmented by genetic predisposition, it is worth noting that effective lifestyle changes remain a very significant strategy to minimize hypertriglyceridemia-associated cardiometabolic disease and death.<sup>14</sup>

The rising profile of a westernized lifestyle (lack/low exercise and higher intake of refined fats) occasioned by western education-associated professions has contributed significantly to the rising profile of MetS and hypertriglyceridemia-associated cardiovascular, metabolic and renal diseases in resource-challenged settings, including Sub-Saharan Africa (SSA).<sup>15</sup> Unfortunately, related literature is rather scarce, further limiting the propagation of educational and awareness campaigns that could lead to lower frequencies of cardiometabolic and renal dysfunction associated with hypertriglyceridemia and uncontrolled glycemic excursions. This study assessed the triglyceride glycemic index (TGI) and determined gender correlates of cardiometabolic and kidney dysfunction in a resource-challenged setting.

## METHODS

### *Study Area*

This hospital-based, cross-sectional analytical study was conducted at two tertiary healthcare institutions: UNIOSUN Teaching Hospital (UTH), Osogbo, and Bowen University



Teaching Hospital (BUTH), Ogbomoso. Both are major teaching hospitals in southwest, Nigeria that provide specialized clinical services, including diabetes care to the local population.

### **Study Design and Sampling Technique**

A systematic random sampling technique was employed to select participants from the diabetes clinics of both hospitals. The study's sampling frame consisted of adults diagnosed with type 2 diabetes mellitus (T2DM) who presented at the clinics over a six-month period. Participants were selected at regular intervals from the clinic registries to ensure a representative sample.

### **Study Population and Eligibility Criteria**

A total of 192 patients with T2DM, comprising 83 males and 109 females, were enrolled in the study after obtaining ethical approvals (NUMBERS: UNIOSUNHREC 2024/0128 and BUTH/REC-72) and informed consent. Eligible participants were adults aged 40 years or older, diagnosed with T2DM after the age of 40, and having received treatment for a minimum of six months.

### **Exclusion Criteria**

To ensure sample homogeneity, individuals with gestational diabetes, pregnant or lactating women requiring tailored glycemic management, and those on hospital admission for acute diabetes-related complications or concurrent chronic conditions were excluded from the study. Patients with known diagnosis of chronic liver disease, end-stage kidney disease, heart failure were also excluded.

### **Sample Size Determination**

The minimum sample size was determined using Fisher's formula,

$N = (Z^2 \times P \times Q) / d^2$ , where:

N is the minimum sample size

Z is the standard normal distribution value corresponding to a 95% confidence level (1.96)

P is the national prevalence of diabetes mellitus in Nigeria (5.77% or 0.0577)<sup>15</sup>

Q is the complementary probability (1-P), equal to 0.9423

d is the specified tolerance for absolute accuracy (3.5% or 0.035)

$N = (1.96)^2 \times 0.0577 \times 0.9423 / (0.03)^2 = 170.5$ .

which yielded a sample size of 170.5.

To account for non-response and missing data, the sample size was increased by 13% to 192.

### **Data Collection**

The study utilized a comprehensive questionnaire to gather detailed information from participants, encompassing demographic characteristics, clinical features, and treatment history. The demographic assessment included age, gender, educational attainment, occupation, and marital status. The questionnaire delved into clinical features, such as the duration of diabetes, and the presence of cardiovascular symptoms, including intermittent claudication, ischemic cardiac pain, and differential body weakness. Renal symptoms, including nocturia, frothy urine, and recurrent facial swelling, were also investigated. Additionally, the type of antidiabetic medications used, concomitant medications, and the presence of comorbidities were recorded, offering a thorough understanding of the participants' demographic and clinical profiles.

### **Physical Measurements and Laboratory Analysis**

Physical measurements, including height, weight, body mass index (BMI), blood pressure, waist circumference, and waist-hip ratio, were obtained using standardized protocols.<sup>16</sup> The ankle brachial index (ABI) which was taken as the ratio of the ankle blood pressure to the brachial blood pressure) was used to diagnose peripheral vascular disease (PVD) with values less than 0.9.<sup>17</sup> To ensure accuracy, all anthropometric measurements were taken following a 12-hour fast,<sup>16</sup> and blood pressure readings were obtained in duplicate, with the mean value used for analysis.<sup>12</sup>

Each patient underwent electrocardiography (ECG) as part of the diagnostic evaluation.<sup>12</sup> Additionally, a 10-millilitre blood sample was collected from each patient through aseptic

venipuncture and subjected to routine laboratory assessments. These assessments included various biochemical markers, such as fasting blood glucose (FBG)<sup>14</sup> and insulin levels,<sup>18</sup> serum creatinine concentrations, fasting lipid profiles,<sup>8</sup> serum folate<sup>18</sup> and vitamin B12 levels,<sup>19</sup> homocysteine<sup>20</sup> and uric acid levels,<sup>21</sup> packed cell volume (PCV),<sup>22</sup> and glycosylated hemoglobin levels<sup>9</sup>. Furthermore, urine samples were analyzed for microalbuminuria using Micral strips,<sup>23</sup> providing valuable insights into the patients' renal function.

### Calculations and Estimations

The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease study equation.<sup>24</sup> Creatinine clearance,<sup>25</sup> insulin resistance,<sup>18</sup> and lipid ratios<sup>26</sup> were also calculated. The atherogenic index of plasma (AIP)<sup>26</sup> and cardiac risk ratio (CRR)<sup>26</sup> were estimated using established formulas. Creatinine clearance was also calculated using a standardized formula.<sup>24</sup>

Insulin resistance was assessed using the Homeostatic Model Assessment (HOMA-IR).<sup>19</sup> Additional calculations included the atherogenic index and lipid ratios.<sup>26</sup>

The Cardiac risk ratio (CRR) was calculated as  $(TC) / HDL-C$ .<sup>26</sup>

The atherogenic index of plasma (AIP) was calculated as  $\log_{10} (TG/HDL-C)$ .<sup>26</sup>

The atherogenic coefficient (AC) was calculated as  $(TC - HDL-C) / HDL-C$ .<sup>26</sup>

The urinary albumin creatinine ratio (UACR)<sup>27</sup> was calculated as  $\text{Urinary albumin (mg/g)} / \text{urinary creatinine (g)}$

Ischemic cardiac pain was defined as left or central chest pain that comes on with strenuous activity and relieved by rest.

### Data Analysis

Data analysis was with the SPSS version 22. Continuous variables as means ( $\pm$ SD) were compared using students t-test, and with more than two groups, a one-way ANOVA was used. Categorical variables (proportions and frequencies) were compared using chi-square or fisher's exact test. In the regression analysis, the unadjusted odds ratios (ORs) were determined to determine the correlates

of the outcome variables. Adjustment variables with  $p < 0.025$  were then entered into the multivariate model to determine anthropometric correlates of study variables.

### Definition of terms

The abnormal values for the parameters are listed below:<sup>8,12,14,16,19,20-26</sup>

The BMI using the National Heart, Lung, and Blood Institute of Health classification.

BMI: Underweight  $< 18.5 \text{ kg/m}^2$ ; normal ( $18.5\text{-}24.9 \text{ kg/m}^2$ ), overweight ( $25.0\text{-}29.9 \text{ kg/m}^2$ ); obesity ( $\geq 30.0\text{-}34.9 \text{ kg/m}^2$ ).

WHR:  $>0.9$  (males),  $>0.85$  (females)<sup>2</sup>

WC:  $>94 \text{ cm}$  (males),  $>80 \text{ cm}$  (females)<sup>2</sup>

Fasting blood glucose (FBG)  $\geq 126 \text{ mg/dl}$

Serum creatinine (SCr)  $\geq 1.2 \text{ mg/dl}$

TC  $\geq 200 \text{ mg/dl}$

TG  $\geq 150 \text{ mg/dl}$

AIP  $\geq 0.1$

TGI ( $TG \times FBG/2$ ) Elevated  $\geq 3.5$ , normal ( $<3.5$ )

AC  $\geq 3.0$

HDL-C  $\leq 40 \text{ mg/dl}$

HbA1c  $\geq 7.0\%$

GFR  $< 60 \text{ ml/min/1.73m}^2$

Elevated Homeostatic model assessment (HOMA-IR)  $\geq 2.5$

Elevated fasting insulin  $\geq 20 \mu\text{U/mL}$  for males and  $\geq 17 \mu\text{U/mL}$  for females.

CRR  $\geq 1.5$

Serum albumin:  $< 3.5 \text{ g/dl}$

UACR  $\geq 2.5 \text{ mg/g}$

Serum folate:  $< 4.5 \text{ ng/mL}$

Serum vitamin B12:  $< 200 \text{ pg/mL}$

Uric acid  $\geq 7.0 \text{ mg/dl}$

Microalbuminuria:  $\geq 30 \text{ mg/24 hours}$ .

Anaemia: Packed cell volume (PCV)  $< 39\%$  (males),  $< 36\%$  (females)

LVH-S wave depth in chest lead 1 plus tallest R wave in chest lead 5 or 6  $> 35 \text{ mm}$  (males) and  $> 33 \text{ mm}$  (females) according to the Sokolow-Lyon criteria<sup>12</sup>

Hyperhomocysteinemia:  $\geq 15 \mu\text{mol/L}$  (males) and  $\geq 13 \mu\text{mol/L}$  (females)

## RESULTS

The mean age of the 192 participants (of which 56.2% were females) was  $60.4 \pm 11.6$  years. The study population was mostly made

up of the middle aged (64.5%). (Table 1). The educational attainments of the participants were: none (4.2%), primary (6.8%), secondary (41.1%) and tertiary (47.9%). Seventy-four percent, 12.5% and 13.5% of the participants used oral hypoglycemic agents (OHAs), insulin and, insulin + OHAs combined, respectively.

**Table 1: Sociodemographic characteristics of the population**

Variables	Frequency	Percentage
<b>Sex</b>		
Males	84	43.8
Females	108	56.2
<b>Age, years</b>		
18-34	3	1.6
35-44	4	2.1
45-54	50	26.0
55-64	74	38.5
65-74	32	16.7
≥75	29	15.1
<b>Marital status</b>		
Single	5	2.6
Married	167	87.0
Co-habiting	25	13.0
Divorced	5	2.6
Widow/widower	13	6.8
<b>Occupation</b>		
Unemployed	58	30.2
Western Paid employment	36	18.8
Artisans/Farmers	54	28.1
Traders	19	9.9
Retired	25	13.0
<b>Duration of diabetes, years</b>		
≤5	96	50.0
6-10	56	29.2
11-15	28	14.6
>16-20	6	3.1
≥21	6	3.1
<b>Smoking</b>		
No	179	93.2
Yes	13	6.8

Hypertriglyceridemia ( $p=0.03$ ) and elevated TGI ( $p=0.32$ ) were more common in the women than men (Table 2). Higher systolic blood pressure ( $p=0.03$ ), higher diastolic blood pressure ( $p=0.03$ ), hyperhomocysteinemia ( $p=0.001$ ) and hyperuricemia ( $p<0.001$ ) were more common in the men than the women.

Ischemic cardiac pain ( $p<0.001$ ), elevated uric acid ( $p=0.001$ ), peripheral vascular disease ( $p<0.001$ ) and elevated FBG ( $p=0.03$ ) were common in participants with elevated TGI (Table 3). Hyperhomocysteinemia and Low HDL-C were more common in participants with elevated TGI ( $p<0.001$  and  $p=0.26$  respectively).

The TGI was positively related with elevated UACR ( $p=0.01$ ) and serum creatinine ( $p=0.02$ ), (Table 4). It was negatively associated with the hematocrit ( $p=0.02$ ) and serum vitamin B12 ( $p=0.01$ ).

Univariate analysis (Table 5) associated the TGI elevation with age  $\geq 65$  years ( $p=0.002$ ), waist circumference-based obesity ( $p<0.001$ ), hypertension ( $p<0.001$ ), hyperhomocysteinemia ( $p<0.001$ ), elevated fasting insulin levels ( $p=0.04$ ), lipid biomarkers of cardiovascular dysfunction ( $p<0.001$ ) and left ventricular hypertrophy ( $p<0.001$ ).

Variables with  $p<0.025$  in the univariate analysis were entered into the multivariate model (Table 6) with backward elimination used to adjust for confounders. This showed waist circumference-based obesity, hypertension, hyperhomocysteinemia, lipid biomarkers of cardiovascular dysfunction and left ventricular hypertrophy as independent predictors of elevated triglyceride glycemic index in T2DM.

## DISCUSSION

The study assessed the triglyceride glycemic index in T2DM in a resource-challenged setting, and determined its correlation with cardiometabolic and kidney function. While higher levels of glycosylated haemoglobin and fasting blood glucose were more in the males, hypertriglyceridemia was more common in the females. The TGI was positively associated with cardiometabolic and kidney functional derangements. The TGI (a product of the serum triglyceride and fasting blood glucose) has been documented to be a better metabolic marker of insulin resistance than the hyperinsulin-normoglycemic clamp.<sup>27</sup>

**Table 2: Gender correlates of clinical findings and laboratory results of participants**

Variables	Total (n, %) Mean $\pm$ SD 192	Males (n, %) Mean $\pm$ SD 84	Females (n, %) Mean $\pm$ SD 108	P-value
<b>Age, years</b>				
<45	7 (3.6)	4 (4.8)	3 (2.8)	
45-64	124 (64.6)	59 (70.2)	65 (60.2)	
$\geq 65$	61 (31.8)	21 (25.0)	40 (37.0)	
<b>Obesity pattern</b>				
BMI, kg/m <sup>2</sup>	49 (25.5)	21 (25.0)	28 (25.9)	0.33
WHR	52 (27.1)	22 (26.2)	30 (27.8)	0.08
WC, cm	53 (27.6)	21 (25.0)	32 (29.6)	0.04
<b>Systolic BP, mmHg</b>	141.1 (11.8)	143.4 (13.2)	138.9 (11.4)	0.03
<b>Diastolic BP, mmHg</b>	88.9 (9.8)	91.1 (8.9)	87.1 (7.8)	0.03
<b>Poor DM control HbA1c</b>	27 (14.1)	12 (14.3)	15 (13.9)	0.25
<b>Poor DM control, FBG</b>	29 (15.1)	14 (16.7)	15 (13.9)	0.07
<b>Elevated HOMA-IR</b>	41 (21.4)	20 (23.8)	21 (19.4)	0.04
<b>Elevated fasting insulin</b>	11 (5.7)	5 (6.0)	6 (5.6)	0.12
<b>Low HDL-C, mg/dL</b>	33 (17.2)	14 (10.7)	19 (17.6)	0.001
<b>Elevated LDL-C, mg/dL</b>	46 (24.0)	21 (25.0)	25 (23.1)	0.06
<b>Elevated TC, mg/dL</b>	21 (10.9)	9 (10.7)	12 (11.1)	0.09
<b>Triglycerides</b>	1.1 (1.0)	1.04 (1.1)	1.6 (1.1)	0.03
<b>Hypertriglyceridemia, mg/dL</b>	41 (21.4)	16 (19.0)	25 (23.1)	0.03
<b>Elevated TGI</b>	46 (24.0)	20 (23.8)	26 (24.1)	0.32
<b>Hyperhomocysteinemia, mol/L</b>	83 (43.2)	44 (52.4)	39 (36.1)	0.001
<b>Hyperuricemia, mmol/L</b>	87 (45.3)	59 (70.2)	28 (25.9)	<0.001
<b>Anaemia</b>	21 (10.9)	10 (11.9)	11 (10.2)	0.31
<b>Microalbuminuria, mg/g,</b>	45 (23.4)	18 (21.4)	27 (25.0)	0.04
<b>Kidney dysfunction,</b>	32 (16.7)	15 (17.9)	17 (15.7)	0.07

FBG-fasting blood glucose, UACR-urine albumin creatinine ratio, SCr-serum creatinine

**Table 3: Cardiometabolic correlates of triglyceride glycemic index in participants**

Variables	Total (n, %) Mean $\pm$ SD 192	Elevated TGI (n, %) Mean $\pm$ SD 46	Normal TGI (n, %) Mean $\pm$ SD 146	P-value
Ischemic cardiac pain	46 (24.0)	27 (58.7)	19 (13.0)	<0.001
Systolic BP, mmHg	141.1 (11.8)	144.6 (14.9)	140.2 (11.9)	0.001
Diastolic BP, mmHg	88.9 (9.8)	93.1 (10.5)	87.6 (8.5)	<0.001
Uric acid, mmol/L	9.7 (2.5)	12.8 (3.3)	8.8 (2.4)	0.001
Homocysteine	17.9 (4.7)	24.6 (7.9)	15.7 (4.1)	<0.001
Triglycerides	1.1 (1.0)	1.7(1.0)	0.9(0.7)	0.01
HDL-C, mg/dL	1.2 (0.8)	1.2 (1.1)	1.3 (1.0)	0.26
LDL-C, mg/dL	1.7 (1.2)	2.1 (1.5)	1.6 (0.8)	0.03
TC, mg/dL	3.9 (1.6)	4.6 (2.3)	3.7 (1.3)	0.002
AIP	0.25 (0.1)	0.45 (0.1)	0.16 (0.1)	<0.001
AC	4.1 (1.7)	6.7 (2.7)	3.3 (1.5)	<0.001
Cardiac risk ratio	6.2 (3.2)	8.6 (4.2)	5.6 (1.9)	0.001
Peripheral vascular disease	18 (39.1)	8 (17.4)	10 (6.8)	<0.001
Left ventricular hypertrophy	36 (78.3)	17 (37.0)	19 (13.0)	<0.001
Glycosylated hemoglobin	6.2 (1.4)	6.9 (2.0)	6.0 (1.4)	0.06
Fasting blood glucose	7.2 (2.5)	8.9 (2.3)	6.8 (1.7)	0.03
Fasting insulin	8.8 (2.6)	10.1 (4.8)	8.4 (2.10)	0.05
HOMA-IR	2.6 (0.8)	3.0 (1.3)	2.5 (0.6)	0.06

TGI-triglyceride glycemic index, BP-blood pressure, HDL-C-high density lipoprotein, LDL-C-low density lipoprotein, TC-total cholesterol, AIP-atherogenic index of plasma, AC-atherogenic coefficient, HOMA-homeostasis model assessment

**Table 4: Renal correlates of triglyceride glycemic index in participants**

Variables	Total (n, %) Mean $\pm$ SD 192	Elevated TGI (n, %) Mean $\pm$ SD 46	Normal TGI (n, %) Mean $\pm$ SD 146	P-value
Nocturia	47 (24.5)	14 (30.4)	33 (22.6)	0.08
Foamy urine (proteinuria)	39 (20.3)	12 (26.1)	27 (18.5)	0.06
Facial swelling	29 (15.1)	9 (19.6)	20 (13.7)	0.05
Systolic BP, mmHg	141.1 (11.8)	144.6 (14.9)	140.2 (11.9)	0.001
Diastolic BP, mmHg	88.9 (9.8)	93.1 (10.5)	87.6 (8.5)	0.04
UACR, mg/g	29.0 (4.5)	38.8 (7.5)	25.8 (5.3)	0.01
SCr, $\mu$ mol/L	92.6 (12.5)	109.6 (18.4)	86.4 (9.2)	0.02
eGFR, mL/min	70.4 (8.3)	60.7 (11.3)	73.9 (6.4)	0.04
Hematocrit	39.8 (7.1)	33.6 (5.4)	41.9 (10.6)	0.02
Albumin	38.6 (8.8)	35.2 (4.9)	39.7 (13.2)	0.05
Folate	14.7 (7.4)	12.4 (6.9)	15.4 (7.9)	0.07
Vitamin B12	354.6 (34.8)	332.7 (26.3)	361.8 (38.5)	0.01

TGI-triglyceride glycemic index, BP-blood pressure, UACR-urine albumin creatinine ratio, SCr-serum creatinine, GFR-estimated glomerular filtration rate, B12-vitamin B12

**Table 5: Univariate analysis of factors associated with elevated triglyceride glycemic index**

Variables	Elevated TGI 46	Normal TGI 146	P-value
<b>Sex</b>			
Males	20 (23.8)	64 (76.2)	
Females	26 (24.1)	82 (75.9)	
<b>Age, years</b>			
<65	21 (16.4)	107 (85.6)	0.002
$\geq$ 65	25 (39.1)	39 (60.9)	
Obesity, BMI	18 (39.1)	31 (21.2)	0.02
Elevated WHR	17 (37.0)	35 (24.0)	0.06
Elevated WC	22 (47.8)	31 (21.2)	<0.001
Hypertension	25 (54.3)	29 (20.0)	<0.001
KD (GFR <60 mL/min)	9 (19.6)	23 (15.8)	0.33
Nocturia	13 (28.3)	34 (23.3)	0.31
Facial swelling	8 (17.4)	21 (14.4)	0.45
Microalbuminuria	13 (28.3)	32 (21.9)	0.06
Hyperglycemia	7 (15.2)	22 (15.1)	0.98
Elevated glycosylated hemoglobin	9 (19.6)	18 (12.3)	0.07
Elevated fasting insulin	4 (8.7)	7 (4.8)	0.04
Insulin resistance	13 (28.3)	28 (19.2)	0.05
Hyperhomocysteinemia	33 (71.7)	50 (34.2)	<0.001
Hyperuricemia, (n, %)	30 (65.2)	57 (39.0)	0.02
Elevated AIP	9 (19.6)	9 (6.2)	<0.001
Elevated atherogenic coefficient	3 (6.5)	5 (3.4)	0.002
Elevated cardiac risk ratio	5 (10.9)	7 (4.8)	<0.001
Left ventricular hypertrophy	14 (30.4)	22 (15.1)	<0.001

BMI-body mass index, WHR-waist hip ratio, waist circumference, KD-kidney dysfunction, ACR-albumin creatinine ratio, AIP-atherogenic index of plasma



**Table 6: Multivariate analysis of predictors of elevated triglyceride glycemic index**

Variables	aOR	95% CI	P-value
Advanced age	1.38	1.05-2.16	0.05
Obesity (BMI)	1.18	1.04-1.98	0.09
Obesity (WC)	3.52	2.66-5.92	0.003
Hypertension	4.63	2.59-5.88	<0.001
Hyperhomocysteinemia	4.16	3.89-5.92	0.002
Hyperuricemia	1.27	0.94-1.63	0.07
Atherogenic index of plasma	5.83	2.47-7.39	<0.001
Elevated atherogenic coefficient, (n, %)	1.36	1.21-2.19	0.05
Cardiac risk ratio	4.35	1.95-5.02	<0.001
Left ventricular hypertrophy	4.08	2.56-5.44	0.002

BMI-body mass index, WC-waist circumference

The higher TGI in the females is contrary to findings by Lelis et al. and Xuan et al. who found higher TGI in males than females but draw similarity with findings by Tian et al who reported that elevated TGI was more predictive of cardiovascular disease- related morbidity and mortality in females than males.<sup>28-30</sup> Higher TGI in females despite the better glycemic control in them (compared to the males) as found in this study suggests a greater contributory role of hypertriglyceridemia than hyperglycemia in TGI trajectory.<sup>31</sup> The peculiar demographics of the study population (females made up 65.6% of the elderly population, whereas the elderly group constituted 31.8% of the entire study population) must, however, be borne in mind.

Menopause has been identified as an independent predictor of insulin resistance, cardiometabolic diseases and adverse outcome.<sup>32</sup> The TGI, a most sensitive and specific marker of IR that is increased in post-menopausal women, partly explains the higher TGI in the females. Moreover, the declining estrogen levels limit estrogens-protective role in cardiometabolic and kidney function.<sup>30</sup> The poor glycemic control that characterizes IR leads to a compensatory hyperinsulinemia which activates an upgraded sympathetic drive leading to higher cardiac output, peripheral vascular resistance and elevated blood pressure.<sup>33</sup> The kidney function derangement (associated with the

vascular effects of elevated TGI found in this study), further reduces the renal clearance of homocysteine. The positive association between hyperhomocysteinemia and, aging (more so in the women) further strengthens the reported higher incidence of hyperhomocysteinemia-associated hypertension (H-type hypertension) in the aged, particularly in post-menopausal women.<sup>34</sup>

Hyperhomocysteinemic cardiovascular dysfunction results from its synergistic effects with hypertriglyceridemia. This synergy is associated with the release of pro-inflammatory cytokines, lipid peroxidation, higher levels of oxidized LDL, lowered HDL-C levels, and macrophagial lipid incorporation. This leads to vascular foam cells accumulation, accelerated atherosclerosis, and higher frequencies of cardiovascular diseases, morbidity and mortality.<sup>34</sup> The combined effects of hyperhomocysteinemia, hypertension, hyperuricemia, kidney dysfunction and, higher LDL-C that were more common in the males, tended to be overwhelmed by the combined effects of obesity, low HDL-C, higher total cholesterol and microalbuminuria, which were more common in the females. Though these factors have been documented to have adverse effects on both cardiovascular metabolic and kidney function, it is worth noting that there seem to be higher specificity of the strength of the correlation between each

of these factors, relating to cardiovascular or metabolic or kidney function.<sup>33-35</sup>

Microalbuminuria-induced podocytopathy with loss of charge, size and shape selectivity induces chronic proteinuria, cupping of the podocytes, renal fibrosis and eventual remodeling.<sup>36</sup> This leads to vasoconstriction-mediated release of inducible nitric oxide (iNO), inhibition of prostacyclin (PGH<sub>2</sub>) and endothelial nitric oxide (eNO) release and, exaggerated stimulation of the renin-angiotensin II aldosterone system and the sympathetic nervous system.<sup>33, 37</sup> This synergy is further enhanced by the higher frequencies of anthropometric derangements and lower HDL-C levels in the females, as HDL-C inhibits lipid peroxidation and LDL-C oxidation, thereby reducing the severity of IR and the atherosclerotic process.<sup>38</sup>

Hypertriglyceridemia and central obesity (that were more common in the females in this study) have been reported to possess lone and synergistic proinflammatory features with heightened IR (higher TGI), further justifying the higher TGI levels in the females, and the more severe IR found in HtH (in association with hypertriglyceridemia) compared with HtH without hypertriglyceridemia.<sup>34, 39</sup>

Although, there were clear gender divergences in the associations with cardiovascular, metabolic, renal and lipid parameters (worse anthropometric and lipid derangements in the females but worse cardiometabolic and renal function derangements in the males), the documented association between elevated TGI and pansystemic tissue/organ dysfunction, supports a greater involvement of hypertriglyceridemia (in association with low HDL-C) in elevated TGI-mediated inflammation.<sup>35, 39, 40</sup> This pansystemic inflammatory role of TGI was reflected in the socio-demographic, metabolic, renal and lipid indices and, cardiovascular dysfunction (typified by left ventricular hypertrophy, an endothelial-based marker of atherogenesis, with higher rates of cardiovascular morbidities and mortalities.<sup>41</sup> This is suggested by the atherogenic index of plasma

and the cardiac risk ratio (in contrast to the atherogenic coefficient) value in predicting elevated TGI, (respectively highlighting the lone contribution of hypertriglyceridemia and low HDL-C in TGI-associated atherogenesis that was more prevalent in the females than males.<sup>39, 40</sup>

**Limitations** encountered included the possible existence of cofounders, the non-inclusion of post-prandial blood sampling which would have been useful in assessing the reported sex-associated differences in pre and post prandial glycemic excursions. The small sample size, the non-inclusion of non-specific inflammatory makers coupled with the mono-ethnic, mono-racial population pattern were also limiting factors. The inclusion of many metabolic measures strengthened the study. Large, multi-ethnic, multi-racial, population-based studies are needed to determine definitive associations of the TGI.

## CONCLUSION

The TGI (a product of the serum triglyceride and fasting blood glucose) is documented to be a very reliable metabolic marker of insulin resistance. An optimized control of hyperhomocysteinemia and MetS in association with lifestyle modification in T2DM is imperative in reducing the TGI and its associated cardiometabolic and renal features.

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