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ORIGINAL RESEARCH

Sex-Specific Comparison Between Triglyceride Glucose Index and Modified Triglyceride Glucose Indices to Predict New-Onset Hypertension in Middle-Aged and Older Adults

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BACKGROUND: Triglyceride and glucose (TyG) index and TyG-related indices combined with obesity-related markers are considered important markers of insulin resistance. We aimed to examine the association between the TyG index and modified TyG indices with new-onset hypertension and their predictive ability stratified by sex.

METHODS AND RESULTS: We analyzed data from 5414 Korean Genome and Epidemiology Study participants aged 40 to 69 years. Multiple Cox proportional hazard regression analyses were conducted to estimate the hazard ratio (HR) and 95% CI for new-onset hypertension according to sex-specific tertile groups after confounder adjustments. To evaluate the predictive performance of these indices for new-onset hypertension, we calculated Harrell's C-index (95% CI). Over a 9.5-year follow-up period, 1014 men and 1012 women developed new-onset hypertension. Compared with the lowest tertile (T) group, the adjusted HR and 95% CI for new-onset hypertension in T3 for TyG, TyG-body mass index, TyG-waist circumference, and TyG-waist-to-height ratio were 1.16 (0.95–1.40), 1.11 (0.84–1.48), 1.77 (1.38–2.27), and 1.68 (1.33–2.13) in men and 1.37 (1.13–1.66), 1.55 (1.16–2.06), 1.43 (1.15–1.79), and 1.64 (1.30–2.07) in women, respectively. The C-indices of TyG-waist-to-height ratio for new-onset hypertension were significantly higher than those of TyG and TyG-body mass index in both men and women.

CONCLUSIONS: TyG and TyG-body mass index were significantly associated with new-onset hypertension only in women. TyG-waist circumference and TyG-waist-to-height ratio were significantly associated with new-onset hypertension in both men and women. A sex-specific approach is required when using TyG and modified TyG indices to identify individuals at risk of incident hypertension.

Key Words: body mass index ■ hypertension ■ triglyceride and glucose index

Hypertension is an important public-health challenge worldwide.[1] In 2019, the global prevalence of hypertension was over 1 billion; a number that doubled since 1990.[2] Globally, elevated blood pressure (BP) is closely associated with mortality from coronary heart disease, stroke, heart failure, and other vascular and renal diseases.[3,4] Numerous studies have verified the benefits of lowering BP in patients with an increased cardiovascular risk.[5]

Insulin resistance (IR), which plays a key role in the development of type 2 diabetes, is involved in the pathogenesis of hypertension and atherosclerotic

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CLINICAL PERSPECTIVE

What Is New?

- TyG-WC and TyG-waist-to-height ratio were significantly associated with new-onset hypertension in both men and women.
- TyG and TyG-body mass index were significantly associated with new-onset hypertension in women but not in men.

What Are the Clinical Implications?

- Sex-specific approaches in using TyG and modified TyG indices as potential indicators for incident hypertension are required to identify individuals who are at risk of developing hypertension.
- Further research should explore the underlying mechanism of sex differences on the effectiveness of TyG indices combining body composition indicators for the prediction of incident hypertension.

Nonstandard Abbreviations and Acronyms

HIEC	hyperinsulinemic-euglycemic clamp
HOMA-IR	homeostatic model assessment of insulin resistance
IR	insulin resistance
TyG	triglyceride and glucose index
WC	waist circumference
WHtR	waist to height ratio

cardiovascular diseases.[6] Therefore, various direct and indirect markers to assess IR have been developed using the hyperinsulinemic-euglycemic clamp test and homeostatic model assessment of IR (HOMA-IR).[7,8] However, the hyperinsulinemic-euglycemic clamp is impractical in clinical practice and epidemiological studies due to the laborious process and high cost.[7] HOMA-IR, based on fasting glucose and insulin, has been validated and is a useful surrogate index to measure IR in clinical application.[8]

The triglyceride–glucose (TyG) index, which is calculated using fasting triglyceride and blood glucose, has been proposed as a simple and available marker for IR to reveal common pathology.[9] Since TyG index was initially used by Simental-Mendia et al in 2008,[10] many studies have recognized that TyG index is associated with an increased risk of hypertension and cardiovascular disease (CVD).[11–17] Recently, TyG-related markers combining TyG and body composition indices, such as body mass index (BMI) and waist circumference (WC), have been shown to have higher predictive performance for metabolic diseases than TyG alone.[18–20]

However, previous studies have investigated the relationship between the TyG index and hypertension in either the general population or specific high-risk groups.[12–16,21] There has been limited research examining this relationship with regard to sex differences.

A recent study reported significant difference in the TyG index between men and women.[22] The study found the combined metabolic indices to be stronger risk indicators for incident type 2 diabetes in women. Specifically, WC and waist-to-height ratio (WHtR) are metrics that represent sex-specific differences in the distribution of body fat. Therefore, we aimed to investigate the relationship between new-onset hypertension and TyG index and modified TyG indices from a combination of easily measurable values, such as BMI, WC, and WHtR in a sex-specific manner. Moreover, we aimed to compare the predictive performance of the TyG index and modified TyG index for new-onset hypertension in the middle-aged and older Korean population.

METHODS

Availability of Data and Materials

Anonymized data and the associated codebook from the KOGES (Korean Genome and Epidemiology Study), conducted by the National Institute of Health and the Korea Disease Control and Prevention Agency in the Republic of Korea, have been made publicly available (https://www.nih.go.kr/ko/main/contents.do?menuNo=300563).

Study Population

A community-based cohort study (KOGES_Ansan_Ansung cohort) was used in the current study. The KOGES_Ansan_Ansung cohort, which consists of adults aged 40 to 69 years, was conducted biennially at the baseline (2001–2002) up to the seventh follow-up (2015–2016). From a total of 10 030 participants at baseline, we included the participants who had at least 1 follow-up during 2003 to 2016 (n=9118). We excluded participants who had hypertension at baseline (n=2995) or incomplete data at baseline (n=1131). Finally, we included a total of 5414 participants in this study (Figure 1). All participants provided written consent and agreed to participate in the study. This study was approved by the institutional review board of Yongin Severance Hospital (IRB No. 9-2022-0090).

Data Collection

Trained medical staff measured the anthropometric variables including height, weight, and WC. Height

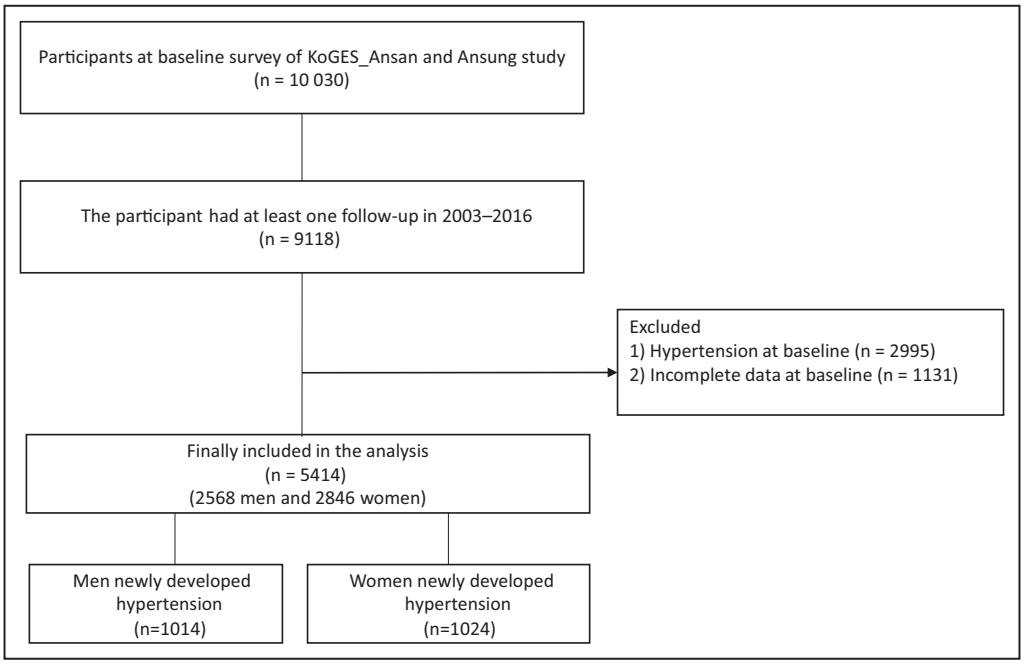

Figure 1. Flow chart of the study population.
KOGES indicates Korean Genome and Epidemiology Study.

and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. BMI was calculated by dividing weight (kg) by height (m) squared. WC was measured with inelastic tape at the midpoint between the iliac crest and lowest rib at the end of normal expiration. WHtR was calculated by dividing WC (cm) by height (cm).

At rest in a seated position, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at least twice at 1-minute intervals. Mercury sphygmomanometer was used for the measurement of BP according to standardized protocol.

Each participant's blood samples were collected after >8 hours of fasting. Fasting plasma glucose (FPG), serum insulin, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and CRP (C-reactive protein) levels were analyzed using the ADVIA 1650 Auto Analyzer (Siemens, Alpharetta, GA) and ADVIA 1800 Auto Analyzer (Siemens). Self-reported questionnaires contained information about smoking status, alcohol consumption, physical activity, drug history, and disease history. Physical activity was measured as metabolic equivalent of task (MET)-hours per week (MET-h/day) using an International Physical Activity Questionnaire.[23] According to the level of physical activity, participants were categorized into 3 groups: (low: <7.5 MET-h/day, moderate: 7.5 to 30 MET-h/day, and high: >30 MET-h/day). Detailed protocol used in KOGES is available at the following website: https://nih.go.kr/ko/main/contents.do?menuNo=300583.

Assessment of Triglyceride Glucose Index and Modified Triglyceride Glucose Indices

$$\text{TyG index} = \text{Ln}\left[\text{TG (mg/dL)} \times \text{fasting glucose (mg/dL)}/2\right].$$[10]

TyG was modified by multiplying with BMI, WC, and WHtR to produce TyG-BMI,[24] TyG-WC,[19] and TyG-WHtR,[20] respectively, as follows:

$$\text{TyG} - \text{BMI} = \text{TyG index} \times \text{BMI}$$

$$\text{TyG} - \text{WC} = \text{TyG index} \times \text{WC}$$

$$\text{TyG} - \text{WHtR} = \text{TyG index} \times \text{WHtR}$$

TyG index and modified TyG indices were categorized into tertiles (T) as follows:

$$\text{TyG, T1: } < 8.357, \text{ T2: } 8.357 - 8.789, \text{ and T3: } > 8.789$$

$$\text{TyG} - \text{BMI, T1: } < 650.886, \text{ T2: } 650.886 - 740.651, \text{ and T3: } > 740.651$$

$$\text{TyG} - \text{WC, T1: } < 193.662, \text{ T2: } 193.662 - 220.832, \text{ and T3: } > 220.832$$

$$\text{TyG} - \text{WHtR, T1: } < 4.048, \text{ T2: } 4.048 - 4.602, \text{ and T3: } > 4.602$$

Definition of Hypertension

Hypertension was defined when at least 1 of the following criteria was met: (1) SBP ≥140 mm Hg, (2) DBP ≥90 mm Hg, (3) treatment with anti-hypertensive medications, or (4) diagnosis by a physician.[25] New-onset hypertension was defined as the occurrence of a hypertension diagnosis during a follow-up period for

individuals who previously had normal blood pressure levels. Right censoring was defined as lost to follow-up or not having developed hypertension by the time of last follow-up. In addition, we defined hypertension according to the 2017 American Heart Association/American College of Cardiology guidelines (SBP ≥130 mm Hg or DBP ≥80 mm Hg).[26]

Statistical Analysis

All data are presented as mean±SD for continuous variables or number (percentage) for categorical variables. Independent 2-sample *t* test or Mann–Whitney *U* test were used to compare the differences in continuous variables between men and women, including age, BMI, WC, WHtR, SBP, DBP, FPG, TC, TG, HDL-C, CRP, and METs. Chi-square test was used to compare the differences in categorical variables between men and women. After testing the interaction between TyG and sex for new-onset hypertension, sex-specific analyses were conducted (*P* for interaction=0.003).

The cumulative incidence rate of new-onset hypertension based on tertiles of TyG and modified TyG indices are presented as Kaplan–Meier curves. Log-rank tests were used to determine whether the cumulative incidence rate of hypertension differed among the tertile groups. Univariable and multivariable Cox proportional hazard regression analyses were performed to calculate the hazard ratio (HR) with a 95% CI for incident hypertension. In Model 1, we adjusted for age. In Model 2, we adjusted for the Model 1 variable plus BMI, physical activity, smoking status, and alcohol consumption. In Model 3, we adjusted for Model 2 variables plus total cholesterol, HDL cholesterol, FPG, CRP, antidiabetic drugs, and antidyslipidemia drugs.

Cox proportional hazard model was also used to determine the dose–response relationship between each TyG, modified and TyG indices and new-onset hypertension. Subgroup analysis for presence of diabetes was conducted to explore if there was an effect modification on the association between TyG, modified TyG, and new-onset hypertension. We also confirmed that all interaction terms for TyG and modified TyG indices and diabetes were significant at a significance level of 0.05. We calculated the Harrell's C-index (95% CI) to evaluate the predictive performance of TyG, TyG-BMI, TyG-WC, and TyG-WHtR for new-onset hypertension. We calculated *P* values for significance of the difference between 2 Harrell's C-indices.[27] All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC) and R software (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at $P<0.05$.

RESULTS

Clinical Characteristics of the Study Population

A total of 5414 participants (2568 men and 2846 women) were included in this study. The mean follow-up period was 9.5 years. Baseline characteristics of the study population based on the presence of new-onset hypertension are presented in Table 1. Among 5414 participants, 2026 (1014 men and 1012 women) individuals

Table 1. Baseline Characteristics of the Study Population According to New-Onset Hypertension

Variable	New-onset hypertension		*P* value
	Yes	No	
No.	2026	3388	
Age, y	52.49±8.74	48.74±7.85	<0.001
Sex, male*	1014 (50.0%)	1554 (45.9%)	0.003
BMI, kg/m^2	24.74±3.10	23.81±2.88	<0.001
Waist circumference, cm	83.43±8.35	79.38±8.17	<0.001
Waist to height ratio	0.52±0.06	0.49±0.05	<0.001
Systolic BP, mm Hg	118.54±10.11	108.51±10.53	<0.001
Diastolic BP, mm Hg	78.67±6.78	72.76±7.84	<0.001
Fasting plasma glucose, mg/dL	87.42±22.16	85.00±18.41	<0.001
Total cholesterol, mg/dL	191.31±35.17	188.40±33.69	0.003
Triglyceride, mg/dL	136 (101–192)	120 (91–165)	<0.001
High-density lipoprotein-cholesterol, mg/dL	44.13±9.63	45.57±10.16	<0.001
CRP	0.14 (0.07–0.25)	0.12 (0.05–0.21)	<0.001
TyG	8.72±0.55	8.57±0.51	<0.001
TyG-BMI	216.09±33.40	204.49±30.56	<0.001
TyG-waist circumference	728.73±97.95	682.10±93.92	<0.001
TyG-waist-to-height ratio	4.56±0.62	4.25±0.58	<0.001
Smoking status*			0.074
Never smoker	1144 (56.5%)	2032 (60.0%)	
Former smoker	311 (15.4%)	498 (14.7%)	
Intermittent smoker	64 (3.2%)	96 (2.8%)	
Everyday smoker	507 (25.0%)	762 (22.5%)	
Alcohol use status			0.449
Never	896 (44.2%)	1558 (46.0%)	
Former	123 (6.1%)	202 (6.0%)	
Current	1007 (49.7%)	1628 (48.1%)	
Metabolic equivalent of task, h/d	25.03±15.26	22.10±13.55	<0.001

BMI indicates body mass index; BP, blood pressure; CRP, C-reactive protein; and TyG, triglyceride and glucose index. *P* values were calculated using the independent 2-sample *t* test for continuous variables. *P* values also were calculated using Mann–Whitney *U* test for triglycerides and CRP.

*Categorical variable represent as number (percent).

developed new-onset hypertension. Participants who developed new-onset hypertension were more likely to be older and men. The values of BMI, WC, WHtR, SBP, DBP, FPG, TC, TG, CRP, and HDL-C differed between participants who developed new-onset hypertension and those who did not. Participants who developed new-onset hypertension had higher levels of TyG, TyG-BMI, TyG-WC, and TyG-WHtR than those who did not develop new-onset hypertension. The proportions of daily smokers and current alcohol consumers were not significantly different between groups. There was a significant interaction between TyG and sex, with a *P* value of 0.003.

Table S1 shows the baseline characteristics of the study population. Mean±SD age was 50.2±8.4 years in men and 50.1±8.4 years in women. The values of WC, WHR, BMI SBP, DBP, FPG, TC, TG, HDL-C, CRP, and METs were significantly different between men and women. The proportions of daily smokers, current alcohol consumers, and those taking antidiabetic drugs were higher in men than in women. The mean levels of TyG, TyG-BMI, TyG-WC, and TyG-WHtR were different between men and women.

Table S2 shows the incidence rate of hypertension according to the follow-up period. The incidence rate of new hypertension was analyzed for men and women biennially. The rates of newly diagnosed hypertension for men and women were the highest in the first 2 years at 11.8% and 9.9%, respectively. Subsequently, after the first 2 years, the incidence rate decreased to 4.6% in men and 4.9% in women.

Longitudinal Relationships Between Triglyceride Glucose Index and Modified Triglyceride Glucose Indices and New-Onset Hypertension

The dose–response relationships between TyG, TyG-BMI, TyG-WC, TyG-WHtR, and new-onset hypertension in both men and women are shown in Figure 2 using the Cox proportional hazard model. A linear relationship between TyG, TyG-BMI, TyG-WC, TyG-WHtR, and new-onset hypertension was observed in men (Figure 2A through 2D) and women (Figure 2E through 2H).

Figure S1 shows the cumulative incidence rate of hypertension in relation to the tertiles of TyG, TyG-BMI, TyG-WC, and TyG-WHtR using Kaplan–Meier curves. T3 of TyG, TyG-BMI, TyG-WC, and TyG-WHtR were associated with a significantly higher incidence of hypertension than the first reference tertile (T1) during the follow-up period in men (log-rank test of TyG, *P*<0.001; log-rank test of TyG-BMI, *P*<0.001; log-rank test of TyG-WC, *P*<0.001; log-rank test of TyG-WHtR,

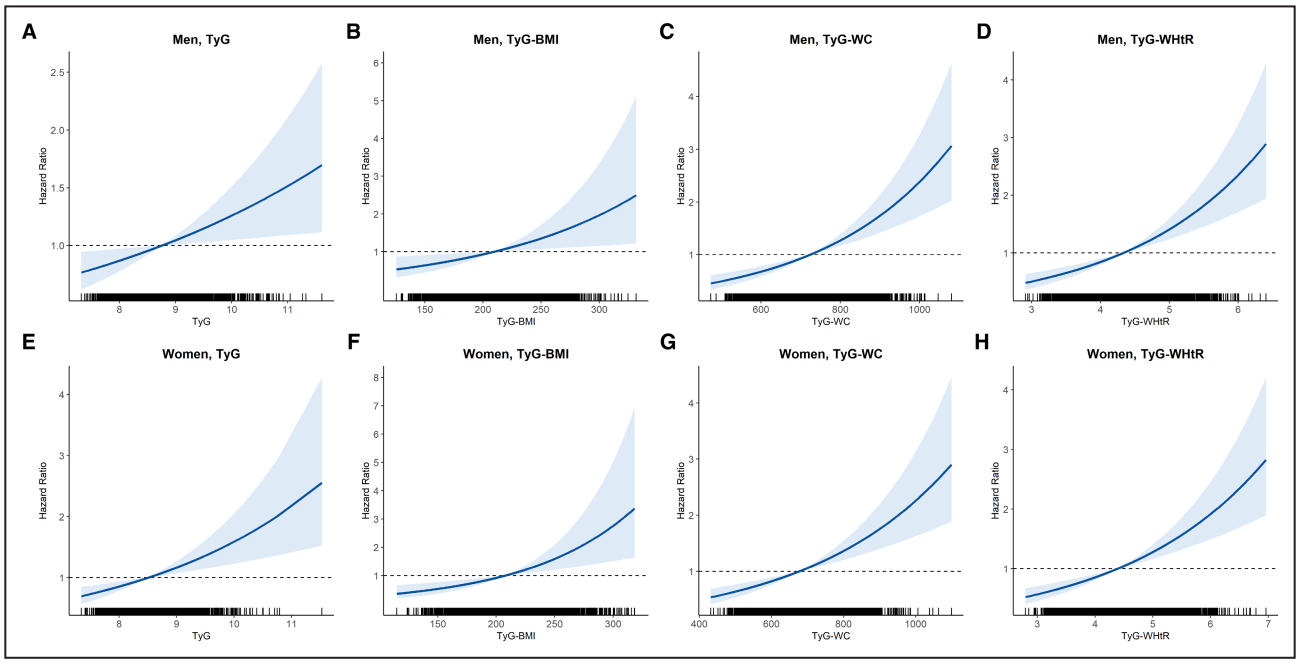

Figure 2. Cox proportional hazards curves showing changes in hazard ratios for incident hypertension with TyG, TyG-BMI, TyG-WC, and TyG-WHtR values.

Relationship between incident hypertension in men and TyG tertile (**A**), TyG-BMI (**B**), TyG-WC (**C**), and TyG-WHtR (**D**). Relationship between incident hypertension in women and TyG tertile (**E**), TyG-BMI (**F**), TyG-WC (**G**), and TyG-WHtR (**H**). The *x* axis is a value of TyG or modified TyG, and *y* axis is the hazard ratio corresponding to the *x* axis value relative to the mean value of TyG or modified TyG. In each panel, the blue line denotes the estimated hazard ratio, and gray shading indicates the 95% confidence intervals. BMI indicates body mass index; TyG, triglyceride-glucose index; TyG-BMI, TyG index×BMI; TyG-WC, TyG index×WC; TyG-WHtR, TyG index×WHtR; WC, waist circumference; and WHtR, waist-to-height ratio.

P<0.001; Figure S1A through S1D). T3 of TyG, TyG-BMI, TyG-WC, and TyG-WHtR were also associated with a significantly higher incidence of hypertension than reference T1 during the follow-up period in women (log-rank test of TyG, *P*<0.001; log-rank test of TyG-BMI, *P*<0.001; log-rank test of TyG-WC, *P*<0.001; log-rank test of TyG-WHtR, *P*<0.001; Figure S1E and S1F).

Table 2 presents the Cox proportional hazard regression model for incident hypertension in relation to the tertiles of each TyG and modified TyG indices in both men and women. In the unadjusted model, the HR (95% CI) for incident hypertension of T3 TyG, when compared with T1, was 1.42 (1.21–1.68) in men and 2.07 (1.78–2.41) in women. TyG was significantly associated with a higher risk of incident hypertension only in women after adjusting for age, BMI, physical activity, smoking, alcohol consumption, TC, HDL-C, FPG, CRP, antidiabetic drugs, and antidyslipidemia drugs (T3 versus T1; HR, 1.37 [95% CI, 1.13–1.66], *P*=0.003 in women; and HR, 1.16 [95% CI, 0.95–1.40], *P*=0.324 in men).

Compared with T1, T3 of TyG-BMI was associated with a higher risk of incident hypertension in both men and women in unadjusted model (HR, 1.69 [95% CI, 1.45–1.97], *P*<0.001 in men; HR, 2.34 [95% CI, 2.00–2.74], *P*<0.001 in women). TyG-BMI was not associated with incident hypertension in men (HR, 1.11 [95% CI, 0.84–1.48]; *P*=0.759) but was significantly associated with incident hypertension in women (HR, 1.55 [95% CI, 1.16–2.06]; *P*=0.011) after adjusting for the same confounders.

Compared with T1, T3 of TyG-WC was associated with a higher risk of incident hypertension in both men and women (HR, 2.16 [95% CI, 1.81–2.59], *P*<0.001 in men; HR, 2.83 [95% CI, 2.43–3.30], *P*<0.001 in women). A significant relationship between TyG-WC and incident hypertension persisted in both men and women after adjusting for confounding variables.

Compared with T1, T3 of TyG-WHtR was associated with a higher risk of incident hypertension in both men and women (HR, 2.17 [95% CI, 1.85–2.54], *P*<0.001 in men; HR, 3.34 [95% CI, 2.82–3.96], *P*<0.001 in women). A significant relationship between TyG-WHtR and incident hypertension persisted in both men and women after adjusting for confounders.

In addition, we also examined the association between HOMA-IR, HOMA-beta (homeostasis model assessment of β-cell function), and incident hypertension

Table 2. Multiple Cox Proportional Hazards Regression Analysis for Incident Hypertension of Tertiles of TyG and Modified TyG Indices

	Hazard ratio with 95% CI							
	Men				Women			
	T1	T2	T3	*P* value	T1	T2	T3	*P* value
TyG								
Unadjusted	1	1.19 (1.00–1.42)	1.42 (1.21–1.68)	<0.001	1	1.37 (1.18–1.59)	2.07 (1.78–2.41)	<0.001
Model 1	1	1.21 (1.02–1.44)	1.49 (1.27–1.76)	<0.001	1	1.13 (0.97–1.32)	1.61 (1.38–1.88)	<0.001
Model 2	1	1.09 (0.92–1.30)	1.20 (1.01–1.43)	0.103	1	1.06 (0.91–1.24)	1.36 (1.16–1.60)	<0.001
Model 3	1	1.08 (0.91–1.30)	1.16 (0.95–1.40)	0.324	1	1.07 (0.91–1.25)	1.37 (1.13–1.66)	0.003
TyG-BMI								
Unadjusted	1	1.29 (1.10–1.52)	1.69 (1.45–1.97)	<0.001	1	1.47 (1.25–1.73)	2.34 (2.00–2.74)	<0.001
Model 1	1	1.37 (1.16–1.61)	1.89 (1.61–2.21)	<0.001	1	1.38 (1.18–1.63)	2.08 (1.78–2.43)	<0.001
Model 2	1	1.10 (0.90–1.33)	1.20 (0.92–1.57)	0.416	1	1.25 (1.03–1.52)	1.61 (1.23–2.10)	0.002
Model 3	1	1.06 (0.86–1.30)	1.11 (0.84–1.48)	0.759	1	1.23 (1.01–1.50)	1.55 (1.16–2.06)	0.011
TyG-waist circumference								
Unadjusted	1	1.41 (1.16–1.70)	2.16 (1.81–2.59)	<0.001	1	1.83 (1.57–2.14)	2.83 (2.43–3.30)	<0.001
Model 1	1	1.46 (1.20–1.76)	2.27 (1.89–2.71)	<0.001	1	1.48 (1.27–1.74)	2.03 (1.73–2.38)	<0.001
Model 2	1	1.28 (1.04–1.57)	1.76 (1.39–2.22)	<0.001	1	1.26 (1.06–1.49)	1.49 (1.21–1.84)	<0.001
Model 3	1	1.29 (1.04–1.59)	1.77 (1.38–2.27)	<0.001	1	1.23 (1.03–1.47)	1.43 (1.15–1.79)	0.006
TyG-waist-to-height ratio								
Unadjusted	1	1.48 (1.26–1.74)	2.17 (1.85–2.54)	<0.001	1	2.21 (1.85–2.65)	3.34 (2.82–3.96)	<0.001
Model 1	1	1.50 (1.27–1.76)	2.18 (1.86–2.56)	<0.001	1	1.80 (1.49–2.16)	2.27 (1.90–2.72)	<0.001
Model 2	1	1.30 (1.09–1.56)	1.69 (1.36–2.10)	<0.001	1	1.54 (1.27–1.87)	1.69 (1.35–2.11)	<0.001
Model 3	1	1.31 (1.08–1.58)	1.68 (1.33–2.13)	<0.001	1	1.53 (1.25–1.86)	1.64 (1.30–2.07)	<0.001

BMI indicates body mass index; and TyG, triglyceride and glucose index. Significance was set at *P*<0.05. Model 1: adjusted for age. Model 2: adjusted for variables used in Model 1 plus BMI, physical activity, smoking status, and current drinker. Model 3: adjusted for variables used in Model 2 plus total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, C-reactive protein, antidiabetes drugs, and antidyslipidemic drugs.

(Table S3). In the unadjusted model, compared with T1, the HR for incident hypertension of T3 HOMA-IR was 1.34 (95% CI, 1.15–1.55) in men and 1.26 (95% CI, 1.08–1.47) in women. The significant associations between HOMA-IR and incident hypertension persisted in Models 1 and 2. After adjusting for age, BMI, physical activity, smoking, alcohol consumption, TC, HDL-C, FPG, CRP, antidiabetic drugs, and antidyslipidemia drugs, theses significant associations were attenuated (T3 versus T1; HR, 1.12 [95% CI, 0.95–1.33] in men; HR, 1.97 [95% CI, 0.91–1.26] in women). There was no significant association between HOMA-beta and incident hypertension.

We additionally showed the results from Cox proportional hazards regression analysis and Harrell's C-index for incident hypertension in relation to the tertiles of TyG and modified TyG indices, using the 2017 American Heart Association/American College of Cardiology definition of hypertension (Tables S4 and S5). The association between TyG and modified TyG indices and new-onset hypertension remained similar even after applying the 2017 definition of hypertension.

Figure S2 shows the subgroup analysis in relation to the presence of diabetes. There were 484 (285 men and 199 women) participants with diabetes and 4930 (2283 men and 2647 women) without diabetes. TyG, TyG-BMI, TyG-WC, and TyG-WHtR were not significantly associated with incident hypertension in both men and women with diabetes. In the group without diabetes, TyG and TyG-BMI were significantly associated with new-onset hypertension only in women without diabetes. TyG-WC and TyG-WHtR were significantly associated with new-onset hypertension in both men and women without diabetes.

Comparison of the Triglyceride Glucose Index and Modified Triglyceride Glucose Indices to Predict New-Onset Hypertension

We identified the Harrell's C-indices of TyG, TyG-BMI, TyG-WC, and TyG-WHtR that were significantly related to incident hypertension in both men and women (Table 3). The Harrell's C-indices in men were 0.549 (95% CI, 0.530–0.567) in TyG, 0.576 (95% CI, 0.557–0.594) in TyG-BMI, 0.595 (95% CI, 0.576–0.613) in TyG-WC, and 0.599 (95% CI, 0.580–0.617) in TyG-WHtR. The Harrell's C-index (95% CI) of TyG-WC was significantly higher than that of TyG (P<0.001) and TyG-BMI (P<0.001) in men. The Harrell's C-index (95% CI) of TyG-WHtR was also significantly higher than that of TyG (P<0.001) and TyG-BMI (P<0.001) in men. However, there was no significant difference in the C-index between TyG-WC and TyG-WHtR. Harrell's C-indices in women were 0.588 (95% CI, 0.570–0.606) in TyG, 0.599 (95% CI, 0.580–0.618) in TyG-BMI, 0.639 (95% CI, 0.622–0.657) in TyG-WC, and 0.650 (95% CI, 0.633–0.668) in TyG-WHtR in women. The Harrell's C-index (95% CI) of TyG-WC and TyG-WHtR was significantly higher than that of TyG (P<0.001 for TyG-WC and P<0.001 for TyG-WHtR) and TyG-BMI (P<0.001 for TyG-WC and P<0.001 for TyG-WHtR) in women, respectively. Out of the 4 indices, the Harrell's C-index of TyG-WHtR was significantly higher than the other indices in women.

DISCUSSION

In the current study, we found that TyG and modified TyG indices (TyG-BMI, TyG-WC, and TyG-WHtR) are significantly associated with new-onset hypertension in women, whereas only TyG-WC and TyG-WHtR are significantly associated with new-onset hypertension in men after adjusting for confounders. The predictive performance of TyG-WHtR for new-onset hypertension was significantly higher than other indices in women, whereas there was no significant difference in the predictive power between TyG-WHtR and TyG-WC in men. The same results were observed even after applying the 2017 American Heart Association/American College of Cardiology definition of hypertension.

TyG index comprising fasting TG and glucose has been identified as a reliable alternative biomarker of IR.[9,11,12] Several epidemiological studies have shown that a higher TyG index is significantly associated with an increased risk of hypertension.[13–17] However, unlike previous studies, we found that the TyG for new-onset hypertension showed poor predictive performance in men (C-index, 0.549 [95% CI, 0.530–0.567]).

Table 3. Harrell's Concordance Index and 95% CIs for Predicting Hypertension Incidence of the TyG, TyG-BMI, TyG-WC, and TyG-WHtR

	Men					Women				
	C-index	95% CI	P1	P2	P3	C-index	95% CI	P1	P2	P3
TyG	0.549	0.530–0.567	Ref			0.588	0.570–0.606	Ref		
TyG-BMI	0.576	0.557–0.594	<0.001	Ref		0.599	0.580–0.618	0.229	Ref	
TyG-WC	0.595	0.576–0.613	<0.001	<0.001	Ref	0.639	0.622–0.657	<0.001	<0.001	Ref
TyG-WHtR	0.599	0.580–0.617	<0.001	<0.001	0.100	0.650	0.633–0.668	<0.001	<0.001	<0.001

BMI indicates body mass index; TyG, triglyceride and glucose index; WC, waist circumference; and WHtR, waist-to-height ratio.

Although the reasons for the differential relationship between the TyG index and new-onset hypertension in men and women are not entirely clear, there are some possible explanations. A greater impact of visceral adipose tissue on CVD risk among women has been reported in previous studies.[22,28] Contribution of visceral lipolysis in the delivery of nonesterified fatty acids to the liver is more significant in women.[21] A previous study also reported more robust correlation between visceral adipose tissue and serum TG in women than in men.[29]

We additionally conducted subgroup analyses to confirm that the results were independent of diabetes status. Modified TyG index was not associated with new-onset hypertension in either men or women with diabetes. There have been inconsistent findings regarding the association between TyG index and CVD. A previous study[30] showed that the cumulative TyG index was significantly associated with the incidence of major adverse cardiovascular events in patient with type 2 diabetes. However, several recent studies did not show significant association between TyG index and CVD and CVD death in patients with diabetes.[31–33] Although the underlying mechanism is unclear, the use of hypoglycemic drugs or insulin could affect the actual blood glucose and blood insulin level. Moreover, diabetes itself may have a greater impact on development of hypertension as an important risk factor.[33] Alizargar et al also suggested that using the TyG index in individuals with CVD could be biased by diabetes and hyperlipidemia.[34] Therefore, the application of TyG as a marker of hypertension should be investigated further while taking sex and underlying glucose status into consideration.

There are several reasons why the TyG and TyG-related indices are associated with incident hypertension. IR serves as the link between the TyG and TyG-related indices and hypertension. Dysregulation in glucose metabolism and disruptions in lipid metabolism are prominent features of IR. Hyperglycemia induces oxidative stress and systemic inflammation, which lead to hypertension by causing endothelial cell dysfuntion.[35] Increased glycosylated products and free radicals lead to decreased nitric oxide production.[35] Reduced bioavailability of nitrous oxide can cause arterial stiffness, which can ultimately result in hypertension.[36] Furthermore, lipid triad under IR status, which is characterized by elevated TG, lowered HDL-C, and appearance of small dense low-density lipoprotein may contribute to the initiation of atherosclerosis.[37]

In the current study, the predictive performances of TyG-WC and TyG-WHtR were greater than those of TyG and TyG-BMI, which was in line with previous studies. One study showed that TyG-WC outperformed the prediction of diabetes compared with that of TyG and TyG-BMI.[19] WC is a useful assessment parameter for abdominal obesity, which is closely associated with disturbances in glucose and lipid metabolism.[38] Visceral adipose tissue secretes proinflammatory cytokines and adipokines, which lead to IR.[39] WC is also significantly associated with increased mortality risk with or without adjusting for BMI.[40] These studies imply that WC may be more effective than BMI for predicting IR and metabolic disturbance. WHtR is also a useful tool for assessing central obesity.[41] WHtR is more sensitive than WC in various ethnic populations and in both sexes, because it adjusts for different statures.[41] A cohort study reported that WHtR is a better predictor for CVD in patients with hypertension than BMI and WC.[42] A 15-year prospective study proved that TyG-related markers that combine obesity markers with TyG index, especially TyG-WHtR, are superior to other parameters in identifying metabolic syndrome in both sexes in an urban Chinese population.[43]

When we further examined the association between HOMA-IR, HOMA-beta, and incident hypertension, the link between HOMA-IR and the incident hypertension weakened after adjusting for confounding factors, and no notable association was found between HOMA-beta and the incident hypertension. Although the precise mechanisms that explain why the TyG index and modified TyG indices outperform HOMA-IR in predicting the new-onset hypertension are not fully understood, IR conditions are believed to not only be confined to impairments in glucose metabolism but also involve abnormalities in fatty acid metabolism resulting from the excessive storage of triglycerides in skeletal muscle.[44] The TyG index appears to indicate IR in both the liver and muscles.[45] Increased levels of TG in the bloodstream can disrupt glucose metabolism in muscle, which is the primary organ responsible for insulin regulation. TG originating from visceral fat stimulate the production of an excessive amount of free fatty acids within the liver, thereby resulting in IR.[46]

A Korean study using the KOGES data set also showed that TyG has superior performance than HOMA-IR in predicting metabolic syndrome.[47] In Son's study, the area under receiver operating characteristic for incident MetS was 0.654 (95% CI, 0.644–0.664) for TyG and 0.556 (95% CI, 0.531–0.581) for HOMA-IR.[47] Wang et al[21] reported that TyG index showed superiority for indicating major adverse cardiovascular events in patients with type 2 diabetes regardless of the use of insulin-related medication.

Our study had several limitations. First, because biochemistry (serum TG and fasting glucose) and body composition indicators were measured in a baseline survey, changes in TyG and modified TyG indices during the follow-up period could not be considered. Second, this study was conducted using a middle-aged and elderly population in Korea; therefore, its results cannot be generalized to other populations. Third, the incidence of hypertension decreased dramatically after the second

follow-up. Although the exact reason for this result is unclear, individuals with new-onset hypertension may have been included in the group lost to follow-up. Also, study participants may also have become more aware of their BP and monitored and managed it through lifestyle modification, which could have led to decreased incidence of hypertension. Despite these limitations, this is the first study to examine the association between TyG and modified TyG index and new-onset hypertension with a large sample size and long-term follow-up period. Additionally, we compared the predictive performances of TyG and modified the TyG index for new-onset hypertension in a sex-specific manner.

CONCLUSION

The current study revealed a significant association between TyG and TyG-BMI and the incidence of hypertension, especially among women. TyG-WC and TyG-WHtR were significantly associated with new-onset hypertension in both men and women. Notably, the combined utilization of TyG and body composition indices such as WC and WHtR exhibited superior predictive performance compared to TyG alone in both men and women. Further research is warranted when employing TyG and modified TyG indices for identifying individuals at risk of developing incident hypertension, while considering sex differences.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S5
Figures S1–S2

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