A novel criterion for identifying metabolically obese but normal weight individuals using the product of triglycerides and glucose

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OBJECTIVES: Metabolically obese but normal weight (MONW) individuals constitute a subgroup of normal weight individuals that display impaired insulin sensitivity with a higher risk of developing diabetes, cardiovascular disease and mortality. We aimed to propose a novel criterion for defining MONW by examining the usefulness and the cutoff value of the TyG index, a product of the levels of triglycerides and glucose, in identifying MONW individuals. In addition, the performance of this criterion in predicting the future incidence of diabetes was assessed.

SUBJECTS/METHODS: A total of 7541 non-diabetic, normal weight (body mass index $\geq 18.5$ and $< 25 \text{ kg m}^{-2}$) subjects were selected from the Korea National Health and Nutrition Examination Survey conducted in 2009–2010. Another 3185 participants with follow-up studies were selected from a prospective community-based cohort study. The TyG index was calculated as $\ln(\text{fasting triglycerides (mg dl}^{-1}) \times \text{fasting glucose (mg dl}^{-1})/2$.

RESULTS: The levels of the TyG index paralleled the prevalence of metabolic syndrome and its components. The cutoff value of the TyG index that reflected MONW based on the receiver operating characteristics analysis was 8.82 for men and 8.73 for women, with the area under the curve values being 0.855 and 0.868, respectively. The sensitivity and the specificity were 84.2 and 77.6% in men and 69.1 and 89.4% in women, respectively. Individuals designated as MONW, who have a normal weight and TyG levels higher than cutoff, displayed a metabolically unhealthy phenotype and an approximately twofold higher risk of developing diabetes compared with metabolically healthy normal weight subjects.

CONCLUSIONS: We propose a simple diagnostic criterion of MONW, which might be used to discriminate subjects with a higher risk of metabolic diseases.

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SUBJECTS AND METHODS

Subjects

Data acquired from two cohort studies were used. The first cohort was a cross-sectional study from the Korea National Health and Nutrition Examination Survey (KNHANES) IV and V, which was conducted in 2009–2010. The Korean Ministry of Health and Welfare and the Korea Centers for Disease Control have conducted the KNHANES periodically since 1998 and annually since 2008. It consists of a health interview survey, a health examination survey and a nutrition survey, which are administered by trained investigators. A rolling sampling design that involves stratified, multistage probability samples is used to collect information that represents the non-institutionalized civilian population in South Korea. Additional details regarding the survey are provided elsewhere.16,17 Among the 14,633 subjects aged 19 years or older who participated in the survey, only non-diabetic, normal weight (BMI ≥ 18.5 and < 25 kg m−2) subjects were selected for analysis. Participants with malignancy, chronic liver disease, renal insufficiency, those who are pregnant and those lacking data for variables included in the analysis were excluded. After excluding the ineligible subjects, the total number of participants for this analysis was 7541 (2987 men and 4554 women). Written informed consent was obtained from all participants, and the institutional review board at The Catholic University of Korea approved this study (No. KC13SISI0796).

To test whether the new criterion for MONW is useful for predicting the development of diabetes, we used the data obtained from the Chungju Metabolic disease Cohort (CMC) study (cohort 2). This study is an ongoing community-based study started in 2003 in a population aged 40 years and over living in the rural area of Chungju City, Korea. Among the 5354 subjects who showed normal baseline fasting glucose tolerance at baseline and had completed their follow-up visit at least once until March 2013 with a median (minimum, maximum) duration of follow-up of 4.6 (4.0, 8.8) years, only normal weight individuals (n = 3185) were selected for the analysis. Additional details regarding this cohort study are described elsewhere.11,16

Measurements

Anthropometric measurements were performed while the participants wore light clothing, and the body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively. The BMI was calculated as the weight (kg) divided by the height (m) squared. The waist circumference (WC) was measured to the nearest 0.1 cm at the level of the midpoint between the iliac crest and the costal margin at the end of a normal expiration. The blood pressure (BP) was measured three times on the right arm with a mercury sphygmomanometer (Baumanometer; Baum, Copagipe, NY, USA) while the subjects were in a seated position after at least 5 min of rest. The final BP value was obtained by averaging the values of the second and third measurements. Hypertension was defined by using the Joint National Committee 7 report as ≥ 140 (systolic BP)/90 (diastolic BP) mmHg or when a participant had used at least 1 pack of cigarettes ever. Subjects who drank 15–30 g per day of alcohol were designated as mild-to-moderate drinkers, and those who drank more than 30 g per day were classified as impaired fasting glucose. In cohort 2, the diagnosis of incident diabetes mellitus was made based on the American Diabetes Association criteria. An oral glucose tolerance test was performed if the fasting plasma glucose level exceeded 5.6 mmol l−1. However, every participant who had followed-up after September 2009 underwent an oral glucose tolerance test, independent of their fasting plasma glucose levels to minimize the possibility of underestimating the incidence of diabetes mellitus.

Definition of MONW

Three different definitions of being ‘metabolically obese’ were used as appropriate in this study. Individuals within a normal BMI (≥ 18.5 and < 25 kg m−2) range (1) having metabolic syndrome (metabolic syndrome criterion), (2) with a TyG index higher than the cutoff value (TyG criterion) or (3) with homeostasis model assessment estimate of insulin resistance in the highest quartile (homeostasis model assessment criterion) were designated as MONW. Subjects not fulfilling these criteria were allocated in the metabolically healthy and normal weight (MHNW) group.

Statistical analysis

All statistical analyses were performed using the SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). The SAS survey procedure was used to account for the complex sampling design and sampling weights of KNHANES and to provide nationally representative prevalence estimates. For the subgroup analysis, a domain analysis was applied to preserve the

Table 1. Baseline characteristics of the study subjects

|                      | Men (n = 2987) | Women (n = 4554) | P      |
|----------------------|---------------|-----------------|--------|
| Age (years)          | 42.5 ± 0.4    | 42.5 ± 0.4      | 0.9524 |
| Height (cm)          | 170.9 ± 0.2   | 158.0 ± 0.1     | < 0.0001 |
| Weight (kg)          | 64.8 ± 0.2    | 53.8 ± 0.1      | < 0.0001 |
| BMI (kg m−2)         | 22.15 ± 0.04  | 21.53 ± 0.04    | < 0.0001 |
| Waist circumference (cm) | 79.2 ± 0.2 | 73.3 ± 0.2      | < 0.0001 |
| Waist-height ratio   | 46.4 ± 0.1    | 46.4 ± 0.1      | 0.5115 |
| Waist (% body fat)   | 20.2 ± 0.2    | 31.5 ± 0.1      | < 0.0001 |
| ASMI (kg m−2)        | 21.5 ± 0.1    | 14.0 ± 0.1      | < 0.0001 |
| ASM/weight (kg/m2)   | 33.2 ± 0.1    | 26.0 ± 0.1      | < 0.0001 |
| Systolic BP (mmHg)   | 116.3 ± 0.4   | 110.9 ± 0.4     | < 0.0001 |
| Diastolic BP (mmHg)  | 76.0 ± 0.3    | 70.9 ± 0.2      | < 0.0001 |
| Fasting glucose (mmol l−1) | 5.11 ± 0.01  | 4.98 ± 0.01     | < 0.0001 |
| Fasting insulin (mmol l−1) | 4.95 (46.8, 50.4) | 51.2 (50.5, 52.0) | 0.0004 |
| HOMA-IR               | 1.86 (1.83, 1.90) | 1.81 (1.85, 1.91) | 0.2873 |
| TC (mmol l−1)        | 4.72 ± 0.02   | 4.70 ± 0.02     | 0.4421 |
| Triglycerides (mmol l−1) | 1.24 (1.20, 1.27) | 0.92 (0.90, 0.93) | < 0.0001 |
| HDL-cholesterol (mmol l−1) | 1.34 ± 0.01  | 1.48 ± 0.01     | < 0.0001 |
| LDL-cholesterol (mmol l−1) | 1.71 ± 0.02  | 2.73 ± 0.02     | 0.4910 |
| TC/HDL ratio         | 3.69 ± 0.03   | 3.30 ± 0.02     | < 0.0001 |
| TG/TC ratio          | 0.95 (0.92, 0.98) | 0.63 (0.62, 0.65) | < 0.0001 |
| TyG                   | 8.53 ± 0.02   | 8.21 ± 0.01     | < 0.0001 |
| IGFBP (ng/ml)        | 19.7 (3.9)    | 10.9 (5.5)      | < 0.0001 |
| Hypertension (%)     | 26.2 (10.5)   | 15.4 (0.7)      | < 0.0001 |
| Metabolic syndrome (%)| 10.5 (7.0)  | 10.8 (0.5)      | 0.7620 |
| Regular exercise (%) | 26.7 (10.0)  | 20.9 (8.3)      | < 0.0001 |
| Energy intake per day (kcal) | 2377 ± 24 | 1709 ± 14       | < 0.0001 |
| Alcohol drinking (%) | 12.5 (7.0)   | 29.9 (0.9)      | < 0.0001 |
| None                  | 71.1 (9.0)   | 68.3 (0.9)      | < 0.0001 |
| Heavy                 | 16.4 (8.0)   | 18.2 (0.8)      | < 0.0001 |
| Smoking (%)           | 24.2 (8.9)   | 89.0 (0.6)      | < 0.0001 |
| Ex-smoker             | 27.7 (4.4)   | 4.4 (0.4)       | < 0.0001 |
| Current smoker        | 48.2 (10.1)  | 66.5 (0.5)      | < 0.0001 |

Abbreviations: ASM, appendicular skeletal muscle; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IGFBP, impaired fasting glucose; LDL, low-density lipoprotein; TC, total cholesterol. Data are expressed as the mean ± s.e., % (s.e.) or geometric means (95% confidence interval).

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complex sampling design, in which entire samples were used to estimate the variance of the subpopulations. The data are expressed as the means ± s.e., as geometric means (95% confidence interval (CI)) or as proportions. If necessary, a logarithmic transformation was performed to achieve a normal distribution. To compare the characteristics of subgroups, an independent sample Student’s t-test or χ²-test was used. The area under the curve and a 95% CI of the receiver operating characteristics curve were calculated to define the cutoff values of the TyG index in identifying MONW individuals. The optimal cutoff values were determined from the maximal Youden’s Index (sensitivity+specificity −1). Multiple logistic regression analysis was used to determine the odds ratios and 95% CI values of cardiovascular risk factors in the MONW subjects, with the MHNW group as the reference category. A log-binomial regression model using Proc GenMod procedure was performed to calculate the relative risk (RR) of MONW in predicting the development of diabetes, with MHNW as the reference category. A P-value < 0.05 was considered significant.

RESULTS
The baseline characteristics of the study subjects are described in Table 1. The mean age and BMI were 42.5 ± 0.4 years and 22.15 ± 0.04 kg m⁻² for men and 42.5 ± 0.4 years and 21.53 ± 0.04 kg m⁻² for women, respectively. The mean blood glucose levels (5.11 ± 0.01 vs 4.98 ± 0.01 mmol l⁻¹, P < 0.0001), geometric mean of TG levels (1.24 (1.20–1.27) vs 0.92 (0.90–0.93) mmol l⁻¹, P < 0.0001) and the TyG index (8.53 ± 0.02 vs 8.21 ± 0.01, P < 0.0001) were significantly higher in men than women.

Impaired fasting glucose and hypertension, but not metabolic syndrome, were more prevalent in men than women. Because significant differences were noted in most of the anthropometric measures, body composition, blood parameters and lifestyle factors between men and women, all further analyses were performed separately.

Next, the prevalence of metabolic syndrome and its components according to the TyG index deciles were analyzed (Figure 1). The percentage of subjects with metabolic syndrome steeply increased from the eighth decile in men and nineth decile in women. This increase paralleled an abrupt increase in the percentage of high TG levels. In contrast, the prevalence of other components of metabolic syndrome gradually increased according to the TyG index deciles. A high BP and low high-density lipoprotein cholesterol level were the most prevalent component in men and women, respectively.

To determine the cutoff value of the TyG index in identifying MONW individuals, a receiver operating characteristics analysis was performed using MONW defined by the metabolic syndrome criterion as a reference (Figure 2). The optimal cutoff value was 8.82 for men and 8.73 for women, with area under the curve (95% CI) values of 0.855 (0.842–0.868) and 0.868 (0.857–0.877), respectively. The sensitivity, specificity, positive predictive value and negative predictive value were 84.2, 77.6, 34.0 and 97.3% in men and 69.1, 89.4, 49.0 and 95.2% in women, respectively. The area under the curve value of the TyG index was significantly higher than that of TG (0.828) or glucose (0.808) in men and that of glucose (0.753) in women.

The gender-specific cutoff values of the TyG index were used to classify participants as MONW or MHNW. The degree of obesity measured by BMI, WC, waist-height ratio and the percentage of total body fat were significantly higher in MONW individuals than in MHNW individuals (Table 2). MONW individuals were more sarcopenic, as revealed by lower levels of the appendicular skeletal muscle and appendicular skeletal

Figure 1. The prevalence of metabolic syndrome and its components according to the TyG index deciles in men (a) and women (b). The numbers on the x axis represents the cutoff values of each decile. BP, blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglyceride; WC, waist circumference.

Figure 2. Receiver operating characteristic curves for the TyG index predicting MONW in men (a) and women (b).
**Table 2. Comparison of the clinical characteristics between MHNW and MONW individuals defined by the TyG criterion**

|                      | Men               | Women              | P     |
|----------------------|-------------------|--------------------|-------|
|                      | MHNW (n = 2089)   | MONW (n = 898)     |       |
| Age (years)          | 40.6 ±0.5         | 47.2 ±0.6          | <0.0001|
| Height (cm)          | 171.3 ±2.0        | 170.1 ±0.3         | <0.0001|
| Weight (kg)          | 64.2 ±2.0         | 66.3 ±0.3          | <0.0001|
| BMI (kg m⁻²)         | 21.85 ± 0.06      | 22.87 ± 0.07       | <0.0001|
| Waist circumference (cm) | 77.8 ± 0.2     | 82.5 ± 0.3         | <0.0001|
| Waist–height Ratio   | 45.4 ±0.1         | 48.6 ±0.2          | <0.0001|
| Body fat (%)         | 19.4 ±2.0         | 22.3 ±0.2          | <0.0001|
| ASM (kg)             | 21.6 ± 0.1        | 21.2 ± 0.1         | 0.0059 |
| ASM/weight (%)       | 33.7 ±0.1         | 32.0 ±0.1          | <0.0001|
| Systolic BP (mmHg)   | 114.2 ± 4.0       | 121.2 ± 2.7        | <0.0001|
| Diastolic BP (mmHg)  | 74.5 ± 0.3        | 79.5 ± 0.5         | <0.0001|
| Fasting glucose (mmol l⁻¹) | 4.99 ± 0.02         | 5.38 ± 0.02         | <0.0001|
| Fasting insulin (pmol l⁻¹) | 47.6 (48.6, 50.4) | 54.3 (52.8, 55.8) | <0.0001|
| HOMA-IR              | 1.76 (1.72, 1.79) | 2.15 (2.09, 2.22)  | <0.0001|
| TC (mmol l⁻¹)        | 4.57 ± 0.02       | 5.08 ± 0.04        | <0.0001|
| Triglycerides (mmol l⁻¹) | 0.92 (0.90, 0.94) | 2.55 (2.47, 2.64)  | <0.0001|
| HDL-cholesterol (mmol l⁻¹) | 1.41 (1.01, 1.03) | 1.16 ± 0.03         | <0.0001|
| LDL-cholesterol (mmol l⁻¹) | 2.71 (2.02, 2.04) | 2.75 ± 0.04         | 0.0004 |
| TC/HDL ratio         | 3.37 ± 0.02       | 4.47 ± 0.06        | <0.0001|
| TyG                  | 0.67 (0.65, 0.69) | 2.21 (2.12, 2.30)  | <0.0001|
| Alcohol drinking (%) | 8.21 ± 0.01       | 9.30 ± 0.02        | <0.0001|
| CHD (%)              | 1.1 (0.2)         | 1.4 (0.4)          | 0.5892 |
| Stroke (%)           | 0.7 (0.2)         | 1.1 (0.3)          | 0.2356 |
| Regular exercise (%) | 27.4 (1.2)        | 25.2 (1.6)         | 0.2827 |
| Energy intake/day (kcal) | 2392 ± 30         | 2340 ± 40          | 0.2811 |
| Smoking (%)          | 13.3 (0.9)        | 10.6 (1.1)         | 0.0001 |
| Mild to moderate     | 72.6 (1.0)        | 67.4 (1.8)         | 0.0001 |
| Heavy                | 14.1 (0.9)        | 22.0 (1.5)         | 0.0001 |
| Current smoker       | 46.2 (1.3)        | 53.0 (2.0)         | 0.0001 |

Abbreviations: ASM, appendicular skeletal muscle; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment criterion of insulin resistance; IFG, impaired fasting glucose; LDL, low-density lipoprotein; MONW, metabolically healthy and normal weight; MHNW, metabolically obese but normal weight; TC, total cholesterol. Data are expressed as the means ± s.e., % (s.e.) or geometric means (95% confidence interval).

**DISCUSSION**

In the current study, we tested the role of the TyG index in identifying MONW subjects. By determining the cutoff value of the TyG index in this context, we propose that individuals with a higher TyG index (above 8.82 for men and 8.73 for women) and normal weight (BMI ≥ 18.5 and < 25 kg m⁻²) can be classified into the MONW group. This novel criterion successfully reflected the metabolic phenotype of MONW and predicted the future development of diabetes.

Recently, subgroups of obesity, such as MONW or metabolically healthy obesity, have gained much interest as their long-term consequences are beginning to be elucidated. Although the notion that metabolically healthy obesity phenotype individuals...
being in the highest quartile or in the specific range of homeostasis model assessment estimate of insulin resistance having excess visceral or body fat showing a decreased glucose disposal rate or having multiple cardiovascular risk factors. These definitions and the clinical characteristics suggest that the main component of MONW is insulin resistance. In this regard, we examined the possibility of using the TyG index, which has been shown to correlate well with other measures of insulin sensitivity, as a simple criterion in defining MONW. Our previous analyses showed that the odds ratios of being categorized into the MONW group increased in a stepwise manner across the TyG index quartiles among normal weight subjects. In this study, we obtained the optimal cutoff values of the TyG index in identifying MONW using the metabolic syndrome criterion as a reference. The receiver operating characteristics analysis showed high area under the curve of receiver operating characteristics values, sensitivity and specificity of the determined TyG cutoff, suggesting that this index is highly predictive. When the participants were divided into MHNW and MONW using the TyG criterion, their clinical characteristics were revealed to clearly differ. A higher metabolic risks and prevalence of impaired fasting glucose, hypertension and metabolic syndrome were noted. Applying the new criterion in a prospective cohort study demonstrated that MONW men and women defined by the TyG criterion were at a significantly higher risk of developing diabetes than MHNW men and women. The TyG criterion outperformed the homeostasis model assessment criterion with a higher RR. Therefore, the TyG criterion might be useful to discriminate individuals with a higher risk of metabolic diseases among apparently healthy-looking normal weight subjects. The most advantageous point of this criterion is that it is an easily calculated measure without the need for complex studies, measuring the BP, WC or serum insulin levels. Hence, it is widely applicable in large epidemiologic studies or in public health management.

The strength of this study is that nationwide survey data involving large number of subjects representing Koreans were analyzed. We further confirmed the performance of the TyG criterion in a prospective community-based cohort study. However, our study features some limitations. First, we did not explore whether MONW individuals defined using the TyG criterion also have higher risk of CVD or mortality. Long-term outcome studies will be needed to elucidate this issue. Second, the CMC study used 40 years old, which limited the interpretation in younger people. Third, because all individuals in this study were Koreans, the applicability and utility of the TyG criterion in other ethnic

Table 3. Odds ratios of cardiovascular risk factors according to metabolic status defined by TyG criterion in normal weight subjects

|                  | Men | Women |
|------------------|-----|-------|
|                  | Crude | Adjusted^* | Crude | Adjusted^* |
| **IFG**          |       |       |       |       |
| MHNW             | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| MONW             | 3.83 (3.06, 4.78) | 2.84 (2.22, 3.63) | 4.56 (3.60, 5.77) | 2.68 (2.08, 3.45) |
| P                | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **Hypertension** |       |       |       |       |
| MHNW             | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| MONW             | 2.81 (2.30, 3.42) | 1.97 (1.58, 2.45) | 3.91 (3.21, 4.77) | 1.50 (1.15, 1.95) |
| P                | <0.0001 | <0.0001 | <0.0001 | 0.0027 |
| **Metabolic syndrome** |       |       |       |       |
| MHNW             | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| MONW             | 22.6 (15.6, 32.7) | 16.4 (11.4, 23.8) | 19.8 (15.1, 25.9) | 12.1 (8.9, 16.5) |
| P                | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Abbreviations: IFG, impaired fasting glucose; MHNW, metabolically healthy and normal weight; MONW, metabolically obese but normal weight. *Adjusted for age, body mass index, regular exercise, alcohol drinking and smoking. Data are expressed as odds ratios (95% confidence interval).

Table 4. Associations of metabolic status defined by TyG criterion or HOMA criterion with the risk of future diabetes in normal weight subjects

|                  | Men | Women |
|------------------|-----|-------|
|                  | Crude | Model 1 | Model 2 | Crude | Model 1 | Model 2 |
| **TyG criterion** |       |       |       |       |       |       |
| MHNW             | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| MONW             | 2.21 (1.49, 3.29) | 2.25 (1.50, 3.38) | 1.69 (1.09, 2.63) | 2.86 (1.90, 4.32) | 2.56 (1.69, 3.90) | 2.55 (1.61, 4.06) |
| P                | <0.0001 | <0.0001 | 0.0191 | <0.0001 | <0.0001 | <0.0001 |
| **HOMA criterion** |       |       |       |       |       |       |
| MHNW             | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) | 1(ref) |
| MONW             | 1.70 (1.11, 2.61) | 1.64 (1.06, 2.55) | 1.62 (1.02, 2.56) | 1.67 (1.08, 2.57) | 1.60 (1.03, 2.48) | 1.64 (1.04, 2.56) |
| P                | 0.0153 | 0.0274 | 0.0393 | 0.0206 | 0.0379 | 0.0319 |

Abbreviations: HOMA, homeostasis model assessment; MHNW, metabolically healthy and normal weight; MONW, metabolically obese but normal weight. Data are expressed as RRs (95% confidence interval). The cutoff value of the highest quartile of HOMA-IR is 1.162 for men and 1.483 for women. Model 1: Adjusted for age and body mass index. Model 2: Adjusted for model 1 + systolic BP, HDL-cholesterol, waist circumference, family history of diabetes, alcohol drinking and smoking.
populations need to be further confirmed. The definitions of overweight and obese status, as well as the TG levels differ across different ethnicities. Furthermore, the susceptibility to metabolic diseases is thought to be higher in Asians for similar degrees of obesity.

In conclusion, our study provides evidence for using the TyG index to identify a metabolically risky subgroup among the normal weight population. Thereby, we propose a novel criterion for defining MONW, which could be widely utilized due to its simplicity, and show its effectiveness in predicting the incidence of diabetes. Outcome studies to evaluate the predictability of this definition on CVD and mortality and confirmation in other cohort studies are warranted. Individualized management via the proper stratification of normal weight individuals according to their metabolic status will be of great importance in the future.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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