

# Markers of insulin resistance and carotid atherosclerosis. A comparison of the homeostasis model assessment and triglyceride glucose index

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## SUMMARY

**Aims:** The present investigation was designed to test the association between carotid atherosclerosis and two simple markers of insulin resistance, i.e. HOMA-Index and TyG-Index. **Materials and methods:** The study was performed in two different cohorts. In the first cohort, 330 individuals were enrolled. Blood pressure, lipids, glucose, waist and cigarette smoking were evaluated. HOMA-IR and TyG-Index were calculated as markers of prevalent hepatic and muscular insulin resistance respectively. Carotid atherosclerosis was assessed by Doppler ultrasonography. The association between cardiovascular risk factors, markers of insulin resistance and carotid atherosclerosis was assessed by multiple logistic regression analyses. In the second cohort, limited to the evaluation of TyG-Index, 1432 subjects were studied. **Results:** In the first cohort, TyG-Index was significantly associated with carotid atherosclerosis in a model including age, sex, diabetes, cigarette smoking and LDL cholesterol, while HOMA-IR was not. When components of metabolic syndrome were added to the model as dichotomous variables (absent/present), TyG-Index retained its predictive power. The same result was obtained when the metabolic syndrome was added to the model (absence/presence). The association between TyG-Index and carotid atherosclerosis was confirmed in the second cohort. **Conclusions:** The present findings suggest that TyG-Index is better associated with carotid atherosclerosis than HOMA-IR.

### What's known

Insulin resistance predisposes to diabetes mellitus, hypertension and dyslipidemia, factors associated with atherosclerosis. It is not known whether insulin resistance associates to atherosclerosis independently of these metabolic alterations.

### What's new

This study demonstrates that peripheral insulin resistance, evaluated through a simple marker such as triglycerides glucose index, associates with carotid atherosclerosis independently of other metabolic alterations and better than markers of hepatic insulin resistance, such as HOMA-Index. The peripheral insulin resistance may be a useful marker of cardiovascular risk.

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### Disclosures

None to disclose.

## Introduction

Insulin resistance predisposes to several metabolic disorders such as hyperglycaemia, hypertension and dyslipidemia, which are strongly associated with atherosclerosis.

Insulin resistance is a complex phenomenon and requires, for its evaluation, sophisticated methods that are not available for use in daily clinical practice (1). For this reason, a number of surrogate markers have been proposed and compared with the gold standard of the hyperinsulinemic euglycemic clamp. Some of these markers have shown predictive value for mortality and morbidity for coronary heart disease. Insulin resistance as estimated by homeostasis model assessment (HOMA-Index) predicts atherosclerosis plaque progression in patients with coronary heart disease in both individuals with and without diabetes (2). Furthermore, the prospective data from the Verona Diabetes Complications Study underline that HOMA-Index is an independent predictor of

CVD in type 2 diabetes (3). Recently, a simple and inexpensive approach to the evaluation of insulin sensitivity has been developed. The test is based on measuring the product of fasting triglycerides and glucose (TyG-Index) and shows a direct correlation with intima-media thickness, HOMA-Index and the hyperinsulinemic euglycemic clamp. Whether and how much surrogate markers of insulin resistance add to the association between risk factors and atherosclerosis has not been clearly established.

Therefore, the purpose of this study was to test whether two simple markers of insulin resistance, i.e. HOMA-Index and TyG-Index, associate with the presence of carotid atherosclerosis and if they give additional information to those of classic cardiovascular risk factors and metabolic syndrome. In the first part of this article, we compared the two indexes of insulin resistance in a group of 330 subjects to test which of the two is the best predictor of carotid atherosclerosis in our population. In the second part, we performed a further investigation to check the

relationship of the only TyG-Index and carotid atherosclerosis in the general population of 1432 subjects.

## Subjects and methods

### Subjects and study design

Subjects enrolled in this study were all participants in a regional Cardiovascular Disease Prevention Campaign. They were all Caucasians and were examined according to a previously standardised protocol (4).

In the first part of this study, 330 subjects were analysed, in whom insulin was measured in addition to traditional cardiovascular risk factors, thus making it possible to calculate HOMA-Index. This part of the study was designed to investigate if and how much surrogate markers of insulin resistance add to the association between classical risk factors and atherosclerosis.

In the second part of the study, 1432 subjects, different from the previous population, were examined according to the same protocol with the exception of plasma insulin, which was not measured. All participants were informed about the aim of the campaign and an informed consent was obtained before examination.

### Cardiovascular risk factors assessment and metabolic status classification

All subjects were examined in the morning in a room at 22 °C, after overnight fasting. Well-trained personnel measured blood pressure, height and weight by routine methods. The mean of two sitting blood pressure readings was used. Body mass index (BMI) was computed as weight (in kilograms) divided by height (in squared metres). Waist circumference was measured midway between the lower rib margin and the iliac crest. A questionnaire was administered to evaluate smoking habit and drug use. Current smokers recorded the number of cigarettes smoked each day. Subjects were asked to record the age at which they started to smoke and those who stopped smoking, also the age at which they gave up. Pack-years of cigarette consumption were calculated from these data assuming that smoking pattern indicated was stable throughout the life. A pack-year was defined as 20 cigarettes a day for a year. Blood was withdrawn from an antecubital vein after echo-Doppler examination. Blood lipids and glucose were measured by commercially available kits. Plasma insulin concentration was determined by a chemiluminescence-based assay (Immulin<sup>®</sup>; Siemens, Milan, Italy). LDL cholesterol was calculated using the Friedewald formula.

Metabolic syndrome (MetS) was defined as the presence of three or more of the following: (i) Waist circumference > 88 cm in women and > 102 cm in men; (ii) Fasting triglycerides  $\geq$  150 mg/dl; (iii) HDL cholesterol < 50 mg/dl in women and < 40 mg/dl in men; (iv) Systolic blood pressure/Diastolic blood pressure  $\geq$  130/85 mmHg or use of antihypertensive drug therapy; (v) Fasting glucose  $\geq$  110 mg/dl or use of hypoglycaemic agents, according to the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) (5).

### Markers of insulin resistance

HOMA-Index was calculated as: fasting plasma glucose (mmol/l)  $\times$  fasting serum insulin (mU/ml)/22.5 (6). The TyG-Index was calculated as: Log [fasting triglycerides (mg/dl)  $\times$  fasting glucose (mg/dl)/2] (7).

### Carotid atherosclerosis assessment

Echo-Doppler examination of carotid arteries (common carotid artery, carotid bulb, internal and external carotid arteries) was performed using an instrument equipped with a 5- to 10-MHz multifrequency high-resolution linear probe, as previously described (8). The subjects were kept in the supine position with their heads slightly extended. Internal, external, bulb and common carotid were examined to evaluate the presence of plaques and/or stenoses. Plaque was defined as localised lesion encroaching the lumen of thickness  $\geq$  1.3 mm, no spectral broadening or only in deceleration phase of systole and systolic peak velocity < 120 cm/s. Stenosis was defined as spectral broadening throughout systole and/or peak flow velocity  $\geq$  120 cm/s. Normal segments were scored 0, those with plaque were scored 1 and those with stenosis were scored 2. A global score was computed by adding the scores of all segments, as previously reported (8). For logistic regression analyses, subjects were classified as with atherosclerosis if they had at least one plaque and/or stenosis in the carotid tree and as without atherosclerosis if they had completely normal echo-Doppler examination.

### Statistical analyses

All statistical analyses were performed by SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). Triglycerides were not normally distributed and were therefore log-transformed.

The correlation between insulin resistance measures was evaluated by Pearson's Correlation test. Student *t*-test was used to compare continuous vari-

ables among women and men. Prevalence in CHD risk factors between sexes was evaluated by chi-squared test. The difference in smoking habit between women and men was tested by the Mann–Whitney test. ANOVA was used to test the difference in cardiovascular risk factors among tertiles of insulin resistance markers.

Logistic regression analysis was used to obtain adjusted estimates of the odds of having carotid atherosclerosis in relation to cardiovascular risk factors, MetS and insulin resistance markers. The logistic regression analysis model was constructed as follows: the variables known to be associated with carotid atherosclerosis (age, sex, cigarette smoking, LDL cholesterol, hypertension and diabetes) were included in a first block; the variables to be tested (indices of insulin resistance and MetS components) were included in a second block. The variables were entered stepwise forward.

## Results

Table 1 shows clinical and biochemical characteristics of subjects enrolled in the first part of the study, according to gender (values are reported as mean  $\pm$  SD, or %). Male subjects were younger, and had an overall worse cardiovascular risk profile (higher waist, fasting plasma glucose, triglycerides and cigarette smoking, lower HDL cholesterol). However, the prevalence of hypertension, obesity and diabetes was similar in the two genders, and MetS was more frequent in female subjects. The prevalence of subjects assuming statin therapy was 8% in female subjects and 6% in male subjects. Male subjects had significantly higher values of TyG-Index, while HOMA-Index was comparable to that of female subjects. Carotid atherosclerosis was also similar in both sexes: 38.5% and 37.8% in men and women respectively.

To test the degree of association between markers of insulin resistance and carotid atherosclerosis, different logistic regression analyses were performed. In all models, sex, age, diabetes mellitus, cigarette smoking, hypertension and LDL cholesterol were present. Independent variables were entered into two blocks. The first block contained the variables known to be associated with carotid atherosclerosis (age, sex, hypertension, cigarette smoking, LDL cholesterol and diabetes). The second block contained HOMA-IR, TyG-Index and MetS components (or MetS *per se*). As shown in Table 2a, TyG-Index added separately to this model was significantly associated with carotid atherosclerosis, while HOMA-Index was not. When the components of MetS were added to the model as dichotomous variables (absent/present),

TyG-Index retained its predictive power and HOMA-Index continued to be not significant. The same result was obtained when the MetS was added to the model (absent/present). When both markers of insulin resistance were included in the model, only the TyG-Index was associated with carotid atherosclerosis. In a second logistic regression analysis, insulin-resistance indices were substituted for by triglycerides (log-transformed), blood glucose and insulinemia. In this model, only triglycerides were independently associated with carotid atherosclerosis (Table 2b) and the addition of MetS components (or MetS *per se*) as dichotomous variables did not alter the finding.

Cardiovascular risk factors were also evaluated in subjects divided according to tertiles of HOMA-Index and TyG-Index (Table 3a and b). As expected, increasing tertiles were characterised by worse risk profile, but subjects in the upper tertile of TyG-Index had less favourable risk factors especially with regard to systolic blood pressure, total and LDL cholesterol and triglycerides. Table 4 shows clinical and biochemical characteristics of subjects enrolled in the second part of the study, according to gender. Again, male subjects were slightly younger, but had an overall cardiovascular risk profile worse than female subjects. They had also higher prevalence of diabetes, but lower prevalence of obesity. The prevalence of subjects assuming statin therapy was 7% in female subjects and 6% in male subjects. Logistic regression analyses, performed in the same way as above reported, confirmed the independent association of TyG-Index with carotid atherosclerosis. Age, hypertension and cigarette smoking were the other variables that significantly entered into the model (Table 5). Neither diabetes nor triglycerides were independently associated with carotid atherosclerosis.

## Discussion

The first part of this study demonstrates that TyG-Index, but not HOMA-Index, associates with carotid atherosclerosis, in a group of 330 subjects. TyG-Index retains its predictive power independently of diabetes and even after adjustment for MetS components or MetS *per se*. The predictive value of TyG-Index is then confirmed in the second part of the study, in a much larger population of 1432 individuals.

As markers of insulin resistance HOMA-Index and the TyG-Index were chosen, mainly for two reasons: first, they are very simple to calculate and thus can be used in daily clinical practice; and second, they probably reflect different aspects of insulin resistance.

The HOMA-Index is calculated based on the values of basal insulin and glucose in plasma. This

**Table 1** Clinical and biochemical characteristics of subjects analysed in the first part of the study

|                                | Males        | Females      | p       |
|--------------------------------|--------------|--------------|---------|
| Number                         | 187          | 143          |         |
| Age (years)                    | 53.0 ± 9.3   | 56.8 ± 7.5   | < 0.001 |
| SBP (mmHg)                     | 131 ± 18     | 133 ± 19     | 0.514   |
| DBP (mmHg)                     | 81 ± 10      | 81 ± 10      | 0.800   |
| BMI (kg/m <sup>2</sup> )       | 28.05 ± 3.85 | 28.69 ± 4.16 | 0.150   |
| Waist (cm)                     | 95 ± 10      | 89 ± 11      | < 0.001 |
| Total cholesterol (mg/dl)      | 238 ± 47     | 243 ± 48     | 0.375   |
| LDL cholesterol (mg/dl)        | 167 ± 45     | 166 ± 44     | 0.910   |
| HDL cholesterol (mg/dl)        | 43 ± 11      | 53 ± 14      | < 0.001 |
| Triglycerides (mg/dl)          | 142 ± 71     | 122 ± 66     | 0.005   |
| Glucose (mg/dl)                | 102 ± 31     | 96 ± 25      | 0.050   |
| Insulin (mU/ml)                | 18 ± 9       | 17 ± 9       | 0.228   |
| Smoking (pack/years)           | 9.87 ± 10.51 | 2.72 ± 6.13  | < 0.001 |
| Hypertension (n, %)            | 85 (45)      | 72 (50)      | 0.379   |
| Obesity (n, %)                 | 48 (26)      | 50 (35)      | 0.670   |
| Diabetes (n, %)                | 18 (10)      | 13 (9)       | 0.869   |
| Metabolic syndrome (n, %)      | 36 (19)      | 44 (31)      | 0.015   |
| Carotid atherosclerosis (n, %) | 72 (39)      | 54 (38)      | 0.891   |
| HOMA-IR                        | 4.52 ± 2.81  | 4.10 ± 3.31  | 0.224   |
| TyG-Index                      | 3.80 ± 0.24  | 3.70 ± 0.25  | < 0.001 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein. Triglycerides were log-transformed before analysis. Smoking was analysed by Mann–Whitney test. Values are expressed as mean ± SD, or %.

**Table 2** Logistic regression analyses. Dependent variable: carotid atherosclerosis (absent/present)

|                           | B     | Exp (B) | 95% CI       | Sig.    |
|---------------------------|-------|---------|--------------|---------|
| <b>(a)</b>                |       |         |              |         |
| Age                       | 0.074 | 1.076   | 1.045–1.109  | < 0.001 |
| LDL cholesterol           | 0.008 | 1.008   | 1.003–1.014  | 0.005   |
| Diabetes (absent/present) | 0.916 | 2.499   | 1.011–6.179  | 0.047   |
| TyG-Index                 | 1.442 | 4.320   | 1.399–12.787 | 0.011   |
| <b>(b)</b>                |       |         |              |         |
| Age                       | 0.074 | 1.077   | 1.045–1.109  | < 0.001 |
| LDL cholesterol           | 0.008 | 1.008   | 1.002–1.014  | 0.005   |
| Diabetes (absent/present) | 1.238 | 3.448   | 1.470–8.088  | 0.004   |
| LnTrig                    | 0.665 | 1.945   | 1.141–3.316  | 0.014   |

(Panel a) Independent variables were entered in two blocks. The first block contained age, LDL cholesterol, gender, cigarette smoking (pack/years), hypertension and diabetes. The second block contained HOMA-Index, TyG-Index and metabolic syndrome components (or metabolic syndrome per se). (Panel b) Independent variables were entered in two blocks. The first block contained age, LDL cholesterol, gender, cigarette smoking (pack/years), hypertension and diabetes. The second block contained LnTriglycerides, blood glucose, insulinemia and metabolic syndrome components (or metabolic syndrome per se). Gender, cigarette smoking and metabolic syndrome components did not enter in both models.

index expresses the ability of basal insulin to suppress hepatic glucose production in fasting conditions and thus reflects mainly insulin resistance in the liver (9). The calculation of HOMA-Index is very simple, even if it requires the dosage of insulin,

which is not always available, especially in the laboratories of developing countries.

The association between HOMA-Index and carotid atherosclerosis has been recently reported by Sourij et al. (10). Interestingly, these authors noted that the

**Table 3** Cardiovascular risk factors according to tertiles of HOMA-Index (a) and TyG-Index (b)

| Tertile                        | 1            | 2            | 3            | p       |
|--------------------------------|--------------|--------------|--------------|---------|
| <b>(a)</b>                     |              |              |              |         |
| Number                         | 110          | 110          | 110          |         |
| Age (years)                    | 54.1 ± 9.0   | 54.3 ± 9.1   | 55.6 ± 8.7   | 0.405   |
| SBP (mmHg)                     | 130 ± 20     | 131 ± 19     | 135 ± 16     | 0.116   |
| DBP (mmHg)                     | 79 ± 9       | 80 ± 10      | 84 ± 10      | < 0.001 |
| BMI (kg/m <sup>2</sup> )       | 26.95 ± 3.42 | 28.05 ± 3.80 | 29.98 ± 4.15 | < 0.001 |
| Waist (cm)                     | 88 ± 8       | 91 ± 10      | 98 ± 12      | < 0.001 |
| Total cholesterol (mg/dl)      | 239 ± 45     | 244 ± 49     | 238 ± 48     | 0.520   |
| LDL cholesterol (mg/dl)        | 161 ± 41     | 172 ± 45     | 166 ± 46     | 0.190   |
| HDL cholesterol (mg/dl)        | 53 ± 14      | 47 ± 13      | 42 ± 10      | < 0.001 |
| Triglycerides (mg/dl)          | 128 ± 72     | 127 ± 64     | 145 ± 71     | 0.038   |
| Glucose (mg/dl)                | 89 ± 13      | 94 ± 15      | 115 ± 41     | < 0.001 |
| Metabolic syndrome (n, %)      | 11 (10)      | 22 (20)      | 47 (43)      | < 0.001 |
| Carotid atherosclerosis (n, %) | 37 (34)      | 35 (32)      | 54 (49)      | 0.015   |
| TyG-Index                      | 3.7 ± 0.22   | 3.7 ± 0.23   | 3.8 ± 0.25   | < 0.001 |
| HOMA-Index                     | 2.2 ± 0.51   | 3.7 ± 0.48   | 7.1 ± 3.8    | < 0.001 |
| <b>(b)</b>                     |              |              |              |         |
| Number                         | 110          | 110          | 110          |         |
| Age (years)                    | 54.3 ± 8.2   | 55.9 ± 8.8   | 53.9 ± 9.1   | 0.185   |
| SBP (mmHg)                     | 128 ± 18     | 133 ± 18     | 134 ± 18     | 0.031   |
| DBP (mmHg)                     | 79 ± 10      | 82 ± 10      | 81 ± 10      | 0.024   |
| BMI (kg/m <sup>2</sup> )       | 27.55 ± 3.93 | 28.45 ± 3.88 | 28.98 ± 4.08 | 0.026   |
| Waist (cm)                     | 89 ± 10      | 93 ± 10      | 96 ± 11      | < 0.001 |
| Total cholesterol (mg/dl)      | 220 ± 44     | 249 ± 43     | 251 ± 49     | < 0.001 |
| LDL cholesterol (mg/dl)        | 153 ± 42     | 178 ± 42     | 167 ± 44     | < 0.001 |
| HDL cholesterol (mg/dl)        | 52 ± 14      | 47 ± 11      | 42 ± 12      | < 0.001 |
| Triglycerides (mg/dl)          | 75 ± 17      | 118 ± 23     | 207 ± 67     | < 0.001 |
| Glucose (mg/dl)                | 88 ± 14      | 96 ± 15      | 114 ± 41     | < 0.001 |
| Metabolic syndrome (n, %)      | 7 (6)        | 17 (15)      | 56 (51)      | < 0.001 |
| Carotid atherosclerosis (n, %) | 31 (28)      | 43 (39)      | 52 (47)      | 0.014   |
| HOMA-Index                     | 3.6 ± 1.8    | 3.9 ± 1.8    | 5.5 ± 4.4    | < 0.001 |
| TyG-Index                      | 3.5 ± 0.11   | 3.7 ± 0.06   | 4.0 ± 0.15   | < 0.001 |

Triglycerides were log-transformed before analysis. Values are expressed as mean ± SD.

association disappeared after adjustment for the presence of MetS, and persisted when adjustment was made for the individual components of the syndrome. However, Sourij et al. did not include in their model the values of LDL cholesterol. In our study, the HOMA-Index was significantly associated with carotid atherosclerosis after adjustment for sex, age and LDL cholesterol (data not shown), but the association disappeared when diabetes, the components of the MetS or the presence of the syndrome were included in the model. In a previous study, in a large population different from that recruited in the present study, we were also not able to demonstrate any association between carotid atherosclerosis and HOMA-Index (11). Furthermore, when the TyG-Index and HOMA-Index were included simultaneously in the regression model, only the former remained significantly associated with carotid atherosclerosis. These data taken

together suggest that the HOMA-Index has a low predictive value for carotid atherosclerosis and probably adds little to the information of the traditional cardiovascular risk factors.

The TyG-Index is even simpler to calculate, based on the product of plasma triglycerides and glucose. A possible increase in triglycerides in plasma would seem able to interfere with the normal metabolism of glucose in the muscle, thereby causing a reduced sensitivity to insulin. Therefore, this index, unlike HOMA-Index, seems to reflect mainly muscle insulin resistance (12–14).

The TyG-Index, unlike HOMA-Index, remained significantly associated with carotid atherosclerosis, even after adjustment for all traditional cardiovascular risk factors. Indeed, the TyG-Index remained in the model while the components of the MetS or the presence of the syndrome was excluded. This result

**Table 4** Clinical and biochemical characteristics of subjects analysed in the second part of the study

|                                | Males        | Females      | p       |
|--------------------------------|--------------|--------------|---------|
| Number                         | 825          | 607          |         |
| Age (years)                    | 52.1 ± 9.5   | 54.4 ± 7.9   | < 0.001 |
| SBP (mmHg)                     | 131 ± 17     | 133 ± 20     | 0.135   |
| DBP (mmHg)                     | 81 ± 9       | 81 ± 9       | 0.726   |
| BMI (kg/m <sup>2</sup> )       | 27.60 ± 3.64 | 28.25 ± 4.58 | < 0.001 |
| Waist (cm)                     | 94 ± 10      | 88 ± 12      | < 0.001 |
| Total cholesterol (mg/dl)      | 227 ± 47     | 235 ± 48     | 0.001   |
| LDL cholesterol (mg/dl)        | 151 ± 46     | 155 ± 46     | 0.081   |
| HDL cholesterol (mg/dl)        | 44 ± 12      | 54 ± 15      | < 0.001 |
| Triglycerides (mg/dl)          | 156 ± 94     | 128 ± 79     | < 0.001 |
| Glucose (mg/dl)                | 106 ± 32     | 99 ± 28      | < 0.001 |
| Smoking (pack/years)           | 9.72 ± 10.95 | 3.28 ± 7.01  | < 0.001 |
| Hypertension (n, %)            | 387 (47)     | 309 (51)     | 0.135   |
| Obesity (n, %)                 | 177 (21)     | 182 (30)     | < 0.001 |
| Diabetes (n, %)                | 95 (11)      | 43 (7)       | 0.005   |
| Metabolic syndrome (n, %)      | 233 (28)     | 160 (26)     | 0.440   |
| Carotid atherosclerosis (n, %) | 305 (37)     | 212 (35)     | 0.384   |
| TyG-Index                      | 3.84 ± 0.26  | 3.73 ± 0.26  | < 0.001 |

Triglycerides were log-transformed before analysis. Smoking was analysed by Mann–Whitney test. Values are expressed as mean ± SD, or %

**Table 5** Logistic regression analyses. Dependent variable: Carotid atherosclerosis (absent/present)

|                   | B     | Exp (B) | 95% CI      | Sig.    |
|-------------------|-------|---------|-------------|---------|
| Age               | 0.080 | 1.083   | 1.068–1.099 | < 0.001 |
| Cigarette smoking | 0.026 | 1.026   | 1.014–1.038 | < 0.001 |
| Hypertension      | 0.517 | 1.676   | 1.323–2.125 | < 0.001 |
| TyG-Index         | 0.466 | 1.594   | 1.015–2.505 | 0.043   |

Independent variables were entered in two blocks. The first block contained age, LDL cholesterol, gender, cigarette smoking (pack/years), hypertension and diabetes. The second block contained TyG-Index and metabolic syndrome components (or metabolic syndrome per se). Gender, LDL cholesterol, diabetes and metabolic syndrome components other than hypertension did not enter in the model.

was confirmed and strengthened in the second part of the study, when the index was tested in a much larger population. Again, the individual components of MetS, and the presence of MetS, were excluded from the model, in which only age, cigarette smoking, hypertension and TyG-Index entered.

This study, to our knowledge, is the first to have investigated the association between carotid atherosclerosis and TyG-Index in a large population. Our results are consistent with those of Vasques et al., who have shown a correlation between TyG-Index and carotid artery intima-media thickness in a small Brazilian population (15).

As an index of atherosclerosis, the presence of plaques in the carotid arteries has been used. The carotid district was chosen because it is easy to be studied non-invasively, by echo-Doppler. Moreover,

the presence of plaques correlates well with the presence of atherosclerosis in other districts, giving an overall estimate of the degree of atherosclerosis (16,17).

The reasons for which the two markers of insulin resistance behave so differently in relation to carotid atherosclerosis can only be hypothesised. Both indexes are strongly correlated with the measurement of insulin sensitivity derived from euglycemic hyperinsulinemic clamp (18,19). They are also correlated with each other, although to a much lesser degree (19). In this study, the correlation between HOMA-Index and TyG-Index was highly significant and of the same order of magnitude as that reported in other studies (7,19). The lower degree of correlation between the two markers, compared with their correlations with euglycemic hyperinsulinemic clamp,



supports the fact that they reflect different aspects of the insulin resistance, and this might cause a different cardiovascular risk profile. For this reason, we have divided subjects enrolled in the first part of the study in tertiles according to HOMA-Index and TyG-Index and have investigated classical cardiovascular risk factors. Participants in the upper tertile of HOMA-Index had significantly higher levels of diastolic blood pressure, BMI, glucose, slightly triglycerides and lower levels of HDL cholesterol. Participants in the upper tertile of TyG-Index had a markedly worse cardiovascular risk profile: higher blood pressure, BMI, total and LDL cholesterol, triglycerides, glucose and lower HDL cholesterol. Overall, increasing tertiles of TyG-Index seem to better capture the increasing levels of cardiovascular risk, compared with HOMA-Index tertiles.

The data of this study might have important clinical implications. The findings support a role for the TyG-Index in the definition of cardiovascular risk, in addition to established risk factors. Indeed, a key concept of modern medicine is to tailor the therapy, according to the global risk. As a consequence, new tools that allow to better evaluate the clinical status of the subjects are mandatory. Many recent intervention studies performed in diabetic subjects have yielded disappointing results (20,21). One possible explanation of this was the lack of adequate risk stratification and the consequent therapeutic target, similar for all the patients. In this context, the TyG-Index might represent a useful marker of severity of disease, providing further information on the 'stage' of disease, and helping the clinician to define the

more appropriate therapeutic strategy. Further investigation on larger sample of subjects and longitudinal studies are needed to establish a cut-off value for TyG-Index, which deserves a more aggressive therapeutic approach.

This index is simple to calculate, requires no additional costs or non-routine tests, and seems more closely related to carotid atherosclerosis also compared with the MetS. If these data are confirmed in future observations, and in other populations, the TyG-Index could become a simple but effective tool for risk assessment in daily clinical practice.

On one hand, the result of this study has many clinical implications; on the other hand, they provide the basis for further research in this field. In this study, a strong relationship between TyG-Index and carotid atherosclerosis, a macro-vascular complication of diabetes, has been demonstrated. Future studies could evaluate a possible relationship also with micro-vascular complications as microalbuminuria, retinopathy or markers of endothelial injury (von Willebrand factor, plasminogen activator inhibitor-1, soluble vascular cell adhesion molecule) indicating the early stage of atherosclerosis.

In conclusion, TyG-Index is better associated with carotid atherosclerosis than HOMA-Index. TyG-Index, expression of insulin resistance mainly localised in the muscle, seems to reflect better the cardiovascular risk profile of the subjects.

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## References

- Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance *in vivo*: advantages, limitations, and appropriate usage. *Am J Physiol Endocrinol Metab* 2008; **294**: E15–26.
- An X, Yu D, Zhang R et al. Insulin resistance predicts progression of de novo atherosclerotic plaques in patients with coronary heart disease: a one-year follow-up study. *Cardiovasc Diabetol* 2012; **11**: 71.
- Bonora E, Formentini G, Calcaterra F et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabetes Care* 2002; **25**: 1135–41.
- Gnasso A, Calindro MC, Carallo C et al. Awareness, treatment and control of hyperlipidaemia, hypertension and diabetes mellitus in a selected population of southern Italy. *Eur J Epidemiol* 1997; **13**: 421–8.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–97.
- Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care* 2004; **27**: 1487–95.
- Simental-Mendia LE, Rodriguez-Moràan M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord* 2008; **6**: 299–304.
- Gnasso A, Irace C, Carallo C et al. In vivo association between low wall shear stress and plaque in subjects with asymmetrical carotid atherosclerosis. *Stroke* 1997; **28**: 993–8.
- Tripathy D, Almgren P, Tuomi T, Groop L. Contribution of insulin-stimulated glucose uptake and basal hepatic insulin sensitivity to surrogate measures of insulin sensitivity. *Diabetes Care* 2004; **27**: 2204–10.
- Sourij H, Schmoelzer I, Dittich P, Paulweber B, Iglseider B, Wascher TC. Insulin resistance as a risk factor for carotid atherosclerosis. A comparison of the Homeostasis Model Assessment and the short insulin tolerance test. *Stroke* 2008; **39**: 1349–51.
- Carallo C, Mancuso G, Mauro G et al. Hepatic steatosis, carotid atherosclerosis and metabolic syndrome: the STEATO Study. *J Gastroenterol* 2009; **44**: 1156–61.
- Katsuki A, Sumida Y, Urakawa H et al. Increased visceral fat and serum levels of triglyceride are associated with insulin resistance in Japanese metabolically obese, normal weight subjects with normal glucose tolerance. *Diabetes Care* 2003; **26**: 2341–4.
- Kelley DE, Goodpaster BH. Skeletal muscle triglyceride. An aspect of regional adiposity and insulin resistance. *Diabetes Care* 2001; **24**: 933–41.
- Pan DA, Lillioja S, Kriketos AD et al. Skeletal muscle triglyceride levels are inversely related to insulin action. *Diabetes* 1997; **46**: 983–8.
- Vasques ACJ, Novaes FS, de Oliveira M et al. TyG Index performs better than HOMA in a Brazilian population: a hyperglycemic clamp validated study. *Diabetes Res Clin Pract* 2011; **93**: e98–100.
- Nambi V, Chambless L, He M et al. Common carotid artery intima-media thickness is as good as carotid intima-media thickness of all carotid artery segments in improving prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. *Eur Heart J* 2012; **33**: 183–90.

- 17 Stein JH, Korcarz CE, Hurst RT et al. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008; **21**: 93–111.
- 18 Bonora E, Targher G, Alberiche M et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment on insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 2000; **23**: 57–63.
- 19 Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab* 2010; **95**: 3347–51.
- 20 Ismail-Beigi F, Craven T, Banerji MA et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet* 2010; **376**: 419–30.
- 21 Duckworth W, Abraira C, Moritz T et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360**: 129–39. Erratum in: *N Engl J Med* 2009; **361**: 1024–1025, 1028.

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