Accuracy of Different Metabolic Syndrome Definitions for Detecting Increased Carotid Intima-media Thickness in Peruvian Type 2 Diabetes Mellitus Subjects without Cardiovascular Disease.

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Abstract

**Background:** To estimate the accuracy of metabolic syndrome definitions for detecting Carotid Intima-Media thickness (CIMT) in Peruvian type 2 diabetes mellitus (T2DM) subjects without cardiovascular events.

**Methods:** We performed a cross-sectional evaluation of T2DM subjects from the endocrinology service of two reference health centers without stroke or coronary disease. Bilateral carotid intima-media thickness was measure by B mode ultrasound one only operator. We performed four definitions of Metabolic Syndrome; 1. Cholesterol Education Program Adult Treatment Panel III (ATP III), 2. Harmonized criteria; 3. Gurka's Metabolic syndrome severity score (MSSS) formula. 4. Non-glucose modified MSSS. We calculated the area under the receiver operator curve (AUROC) for detecting increased CIMT (≥ 0.86 mm) between metabolic syndrome definitions.

**Results:** We included 184 subjects with T2DM, 29% were men with a mean age of 61.5 ± 10.5 years old. Median diabetes time was 10.8 years (IQR 4.8 to 19.4), and 26.8% achieved HbA1c goals. Non-glucose modified MSSS was the only definition significantly correlated with elevated CIMT (r = 0.19; p<0.01), and it showed the best accuracy for predicting elevated CIMT (AUC: 0.61, CI95%: 0.52-0.70). Adjusting for age, sex, and HbA1c, each point increase in the non-glucose MSSS Z score, the risk of altered CIMT increases by 59% RP 1.59 (CI 95% 1.09 - 2.35; p=0.017).

**Conclusions:** Non-glucose modified MSSS had a weak accuracy for elevated CIMT and was the best compared to ATP III, harmonized, and original MSSS. Further research on no MS-factors is required to predict better elevated CIMT.

1. **Background**

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in subjects with T2DM worldwide, and physicians call coronary equivalent to that subject with diabetes mellitus without coronary disease due to the high burden of disease. Subclinical cardiovascular disease (SCVD) determination, through Carotid intima-media (CIMT), coronary artery calcium (CAC), and presence of carotid plaque (CP), is associated with overt CVD, and this structural surrogate helps establish preventive strategies in primary care. Although CIMT has a lower predictive ability to detect overt CVD than CAC and CP (1), it might be considered the earliest structural change compared to the other subclinical parameters.

Metabolic syndrome (MS) is the aggregation of factors that include three of five components: waist circumference, glucose, HDL-cholesterol, triglycerides, and blood pressure (2). There are multiple definitions, varying by the cut-off points or one factor's predominance over another (2–4). Both T2DM and MS are associated with an increased prevalence of SCVD and overt CVD (5).

Furthermore, the reduction or aggregation of factors does not necessarily determine lower or higher cardiometabolic risk. Gurka et al. (7) designed a continuous score for the severity of metabolic syndrome
specific to sex and ethnic group. According to factor analysis models, the metabolic syndrome severity score (MSSS) offers the advantage of converting those dichotomous variables (present or absent) into continuous numerical variables. This severity score has shown a good correlation with risk markers such as insulin, adiponectin (8), and predictive value for cardiovascular risk in T2DM subjects (9), and chronic kidney disease (10).

For these reasons, it is critical to determine whether MSSS can predict the SCVD through the CIMT measurement and to clarify if this method could be used as an early tool for preclinical CVD. The absence of SCVD seems to attenuate the risk of overt CVD in subjects with T2DM and MS (6). Thus, we propose evaluating the accuracy of MSSS and other metabolic syndrome definitions to detect increased carotid intima-media thickness in Peruvian Type 2 diabetes mellitus subjects without CVD attending to a healthcare network social security system.

2. Methods

2.1 Study design.

The study was conducted as a cross-sectional design. All subjects gave written informed consent, and the study procedure followed the Helsinky Declaration's agreements and was approved by the institutional ethics committee.

2.2 Patient

A total of 184 subjects with Diabetes mellitus were recruited from the outpatient clinic of the Edgardo Rebagliati Martins Hospital (HNERM) and the Diabetes and Hypertension Center (CEDHI) of the Social security Health System between January 2019 and January 2020. We included subjects older than 20 years and diagnosis of DM based on the ADA criteria. Those patients with a history of coronary artery disease, stroke, peripheral revascularization, or major amputation due to peripheral arterial disease were excluded. Likewise, those with DM1, LADA, NYHA III or IV heart failure, Child B or C liver disease, glomerular filtration rate < 60 ml/min, acute or previous disease up to a range of 6 months, surgery & radiotherapy at the cervical level and use of immunosuppressants or corticosteroids.

2.3 Clinical and biochemical parameters

Independent, trained medical personnel evaluated and collected data patients. Vital functions and anthropometric measurements were taken according to the established protocol. Waist circumference was measured with a tape scale according to the International Diabetes Federation (IDF) recommendations. A questionnaire was filled out directly from the patient regarding pathological history, lifestyle, comorbidities, and pharmacological treatment.

We obtained fasting blood samples for biochemical analyzes that included glucose, HbA1c, and lipid profile. The process was according to the central laboratory's routine method.
We defined Metabolic syndrome according to ATP III and harmonized criteria and use the cut-off for abdominal perimeter obtained by Aschner in the harmonized MS criteria. We calculated MSSS (7) and non-glucose MSSS, according to Gurka et al (9), as Z-score through a spreadsheet.

2.4 Measurement of MICT

We measured CIMT by a single trained physician independent of data collection and processing using a Toshiba Nemio XG ultrasound scanner. We used a B-mode carotid ultrasound with a 7.5 MHz linear transducer to assess the CIMT with standard insonation parameters. Patients were examined supine with the neck hyperextended and identified three segments in the anterior and posterior plane: 1 cm distal to the common carotid proximal to the carotid bifurcation, the bifurcation itself, 1 cm proximal to the internal carotid artery. We obtained the maximum average CIMT value from the far wall of both the right and left common carotid arteries and excluded CIMT ≥ 1.5 mm

2.5 Statistical analysis

We presented categorical data as absolute and relative frequencies and consecutive data as mean and standard deviation or medians with interquartile range according to normal distribution. We described CIMT according to sex and age.

Also, we show the correlation between each SM definition with CIMT through Pearson's coefficient and its scatter charts. A value of $p < 0.05$ was considered significant.

We performed area Under the Receiver Operator Curve (AUROC) of each MS definition to predict CIMT ≥ 0.86 mm, and we calculated sensitivity and specificity according to the optimal cut-off value for each MS definitions.

We made a bivariate analysis for related and no related MS factors for CIMT and a regression model A adjusted to age and sex, and a regression model B adjusted to age, sex, and HbA1c.

3. Results

This study included 184 subjects with T2DM 29% were men with a mean age of 61.5 ± 10.5 years old. Median diabetes time was 10.8 years (IQR 4.8 to 19.4) with a median HbA1c of 8.1% (IQR 6.9 to 9.85), and only 26.8% achieved HbA1c goals. Smoker and sedentary lifestyle prevalences were 18.4% and 73.9%, respectively. Antihypertensive drugs were used by 48.4% for used drugs, statins by 46.7%, and acetylsalicylic acid by 27.7%. Obesity prevalence was 42.3%, with a median waist circumference of 98 cm (IQR 89.7–104). (Table 1)
| Clinical-epidemiological characteristics in subjects with diabetes mellitus without cardiovascular disease at the Edgardo Rebagliati Hospital. |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Total N = 184                                   | Female N=131    | Male N=53       |
| Epidemiological                                 |                 |                 |
| Age, mean (SD)                                  | 61.5 ± 10.5     | 60.4 ± 10.6     | 64.4 ± 9.9      |
| Diabetes time, median (IQR)                     | 10.8 (4.8 to 19.4) | 10.5 (4.7 to 17.7) | 11.8 (5.5 to 22.2) |
| Smoker, n(%)                                    | 34 (18.4)       | 18 (13.7)       | 16 (30.2)       |
| Sedentary lifestyle, n(%)                       | 136 (73.9)      | 31 (23.7)       | 17 (32.1)       |
| Drugs                                           |                 |                 |                 |
| Antihipertensive, n(%)                          | 89 (48.4)       | 60 (45.8)       | 29 (54.7)       |
| Statins, n(%)                                   | 86 (46.7)       | 61 (45.6)       | 25 (47.2)       |
| Acetylsalicilic acid, n(%)                      | 50 (27.7)       | 30 (22.9)       | 20 (37.7)       |
| Metformin, n(%)                                 | 166 (90.2)      | 116 (88.6)      | 50 (94.3)       |
| Glyburide, n(%)                                 | 34 (18.5)       | 24 (18.3)       | 10 (18.9)       |
| SGLT2 inhibitor, n(%)                           | 1 (0.5)         | 0 (0.0)         | 1 (1.9)         |
| GLP1 agonist, n(%)                              | 1 (0.5)         | 1 (0.0)         | 0 (0.0)         |
| Insulin, n(%)                                   | 69 (37.5)       | 50 (38.2)       | 19 (35.9)       |
| Clinical                                        |                 |                 |                 |
| Body mass index (kg/m^2), median (IQR)          | 28.8 (25.7 to 32.2) | 28.9 (25.8 to 32.2) | 28.6 (25.2 to 32.4) |
| BMI >30 kg/m2, n(%)                             | 72 (42.3)       | 51 (42.9)       | 21 (41.2)       |
| Waist circumference (cm), median (IQR)          | 98 (89.75 to 104) | 100 (91 to 105) | 97 (88 to 104)  |
| Blood pressure >130/85, n(%)                    | 83 (45.1)       | 63 (48.1)       | 20 (37.7)       |
| Glycemia (mg/dl), median (IQR)                  | 135 (106 to 193) | 143 (106 to 213) | 131 (106 to 153) |
| Triglycerides, median (IQR)                     | 163 (107.5 to 224) | 170 (118 to 244) | 138 (101 to 196) |
| Total Cholesterol (mg/dl)                       | 178.5 (151 to 212) | 189 (161 to 215) | 158 (133 to 195) |
| HDL cholesterol (mg/dl), median (IQR)           | 45 (39 to 52)   | 48 (41 to 54)   | 40 (34 to 48)   |
| LDL cholesterol (mg/dl), median (IQR) | 110 (89 to 139) | 116.5 (94 to 142) | 101 (75 to 123) |
|---------------------------------------|-----------------|-------------------|-----------------|
| Glomerular filtration (ml/min/24 h), median (IQR) | 105.3 (87.6 to 116.7) | 108.3 (96 to 117) | 94 (85 to 106) |
| A1C (%), median (IQR) | 8.1 (6.9 to 9.85) | 8.2 (6.9 to 10.1) | 8 (6.85 to 9.4) |
| A1c < 7% | 48 (26.7) | 34 (26.6) | 14 (26.9) |
| Metabolic syndrome | | | |
| ATP III criteria, n(%) | 135 (73.4) | 86 (65.7) | 49 (92.5) |
| Harmonizing criteria, n(%) | 145 (78.8) | 96 (73.3) | 49 (92.5) |
| MSSS | | | |
| Z-score MSSS, median (IQR) | 1.34 (0.58 to 2.71) | 1.78 (0.70 to 3.28) | 0.84 (0.46 to 1.48) |
| Z-score MSSS ≥ 0 , n(%) | 110 (59.8) | 119 (90.8) | 47 (88.7) |
| Z-score non-glucose MSSS, median (IQR) | -1.08 (-1.54 to -0.54) | -1.30 (-1.66 to -0.89) | -0.43 (-0.91 to -0.19) |
| Z-score non-glucose MSSS ≥ 0 , n(%) | 8 (4.3) | 1 (0.7) | 7 (13.2) |
| CIMT (mm), Median (IQR) | 0.8 (0.7 to 0.9) | 0.75 (0.7 to 0.85) | 0.85 (0.7 to 0.95) |
| ≥ 0.86 mm, n(%) | 54 (29.4) | 32 (24.4) | 22 (41.5) |

IQR Interquartile range, SD Standard deviation, HDL high-density lipoprotein, LDL low-density lipoprotein, SGLT2 Sodium-glucose cotransporter-2; GLP1 glucagon-like peptide-1; ATP III: Adult treatment Panel III. CIMT: carotid medial intima thickness

Metabolic syndrome for ATP III criteria and Harmonized criteria were 73.4% and 78.8%, respectively. The Median Z-score of the MSSS was 1.34 (IQR 0.58 to 2.71), and the median Z-score of the non-glucose MSSS was -1.08 (IQR -1.54 to -0.54). The prevalence of MSSS and non-glucose MSSS above Z-score ≥ 0 were 59.8% and 4.3%, respectively. (Table 1)

Median CIMT was 0.8 mm (0.7–0.9), and the prevalence of elevated CIMT, defined by Rizzo (≥ 0.86 mm), was 29.4%. CIMT tends to increase according to age in both sexes (Fig. 1)

Only non-glucose MSSS showed a correlation with CIMT. (r = 0.19, p < 0.01). (Fig. 2). Non-glucose MSSS obtained the best AUROC 0.61 (0.52–0.70) compared with the other definitions. (Fig. 3). MSSS and Harmonized SM criteria included 0.5 in their confidence interval. A Z-score of -1.0 was the best cut-of
point of non-glucose MSSS to predict elevated CIMT. This value had 57.4% and 60% of sensitivity and specificity, respectively. (Table 2)

Table 2
The area under the ROC of the Metabolic Syndrome Severity Score and Classic Definitions of Metabolic Syndrome for carotid medial intima thickness in Subjects with Diabetes Mellitus without Cardiovascular Disease at the Edgardo Rebagliati Martins Hospital.

|                          | AUC ROC  | Optimal cut-off | Sensitivity | Specificity |
|--------------------------|----------|-----------------|-------------|-------------|
| Metabolic syndrome       |          |                 |             |             |
| ATP III MS criteria      | 0.59 (0.51 to 0.68) | 4              | 44.4%       | 71.5%       |
| Harmonizing MS criteria  | 0.56 (0.47 to 0.65) | 4              | 53.7%       | 59.2%       |
| Metabolic Syndrome Severity Score |          |                 |             |             |
| MSSS                     | 0.48 (0.39 to 0.57) | 0.30           | 87.0%       | 20%         |
| Non-glucose MSSS         | 0.61 (0.52 to 0.70) | -1.00          | 57.4%       | 60%         |

MS ATP III: 3 of 5 criteria according to Adult Treatment Panel III. MS Harmonizing criteria: : 3 of 5 criteria according to Harmonized Consensus.

Only systolic pressure was associated with CIMT (PR 1.01 CI95% 1.01 to 1.03; p < 0.000) of the metabolic syndrome factors. Age, male sex, and the use of hypertensive drugs also showed association with CIMT (Table 3).
Table 3
The prevalence rate of factors associated with elevated carotid medial intima thickness in subjects with diabetes mellitus without cardiovascular disease at the Edgardo Rebagliati Martins Hospital.

|                                    | PR   | CI 95%     | P      |
|------------------------------------|------|------------|--------|
| **Metabolic Syndrome factors**     |      |            |        |
| Glycemia (mg/dl)                   | 0.99 | 0.99–1.00  | 0.52   |
| Waist circumference (cm)           | 1.00 | 0.98–1.02  | 0.56   |
| HDL cholesterol (mg/dl)            | 0.98 | 0.96–1.01  | 0.12   |
| Triglycerides (mg/dl)              | 1.00 | 0.99–1.00  | 0.33   |
| Systolic blood pressure (mmHg)     | 1.01 | 1.01–1.03  | 0.000  |
| **Other factors**                  |      |            |        |
| Age (years old)                    | 1.06 | 1.03–1.09  | 0.000  |
| Male sex                           | 1.69 | 1.09–2.63  | 0.018  |
| Smoker                             | 1.12 | 0.65–1.95  | 0.66   |
| Diabetes time (years)              | 1.01 | 0.99–1.03  | 0.12   |
| Body mass Index (kg/m2)            | 0.99 | 0.95–1.05  | 0.99   |
| A1c (%)                            | 0.95 | 0.86–1.06  | 0.41   |
| Total cholesterol (mg/dl)          | 1.00 | 0.99–1.01  | 0.95   |
| LDL cholesterol                    | 0.99 | 0.99–1.00  | 0.86   |
| Hypertension drug                  | 2.13 | 1.31–3.47  | 0.002  |
| Statins drug                       | 0.72 | 0.45–1.15  | 0.17   |

PR: Prevalence rate. CI95% Confidence Interval 95.

*aUnivariate regression using generalized linear model with robust variance and poisson distribution. A value of 0.86 mm is considered as anormal carotid medial intima thickness.

In the crude analysis, each point increase in the non-glucose MSSS Z score, the risk of altered CIMT increases by 55% PR 1.55 (CI95% 1.05 to 2.28). Adjusting for age, sex, and HbA1c, MSSS also showed association PR 1.59 (CI 95% 1.09 to 2.35; p = 0.017). (Table 4)
Table 4
Multivariate analysis of the severity score of metabolic syndrome without glycemia for the thickness of the medial carotid intima-media in subjects with diabetes mellitus without cardiovascular disease at Hospital Edgardo Rebagliati.

|                  | Bivariate | Multivariate model 1<sup>a</sup> | Multivariate model 2<sup>b</sup> |
|------------------|-----------|----------------------------------|----------------------------------|
|                  | PR        | Ci 95%                           | P                                | PR        | Ci 95%                           | p        | PR        | Ci 95%                           | P        |
| Non-glucose MSSS | 1.55      | 1.05–2.28                        | 0.01                             | 1.54      | 1.07–2.22                        | 0.02     | 1.59      | 1.09–2.35                        | 0.017    |
| (Z score)        |           |                                  |                                  |           |                                  |          |           |                                  |          |
| Age (years old)  | 1.06      | 1.03–1.09                        | <0.000                           | 1.06      | 1.04–1.09                        | <0.000   | 1.06      | 1.04–1.09                        | <0.000   |
| Male             | 1.69      | 1.09–2.63                        | <0.018                           | 0.95      | 0.57–1.57                        | 0.84     | 0.91      | 0.55–1.50                        | 0.71     |
| A1c (%)          | 0.95      | 0.86–1.06                        | 0.41                             |           |                                  |          |           |                                  |          |
|                  |           |                                  |                                  |           |                                  |          |           |                                  |          |

PR: Prevalence rate. CI95% Confidence Interval 95%. MSSS: Metabolic syndrome severity score.

<sup>a</sup>Multivariate regression using a generalized linear model with robust variance and Poisson distribution. A value of 0.86 mm is considered as abnormal carotid medial intima thickness.

<sup>b</sup>Model 1: Adjusted to age and sex. Model 2: Adjusted to age, sex, and A1c.

4. Discussion

MSSS is a prediction model developed from the National Health and Nutrition Examination Survey (NHANES) database. It must be convenient to validate outcome studies in different populations such as Latin American subjects to answer whether this prediction model can predict subclinical atherosclerosis as an early marker of CV events. In the present study, only the non-glucose MSSS definition showed the best diagnostic discrimination for elevated CIMT and presented a weak performance. The original MSSS did not show any discrimination in this population.

MSSS performed a significant association with future CVD among type 2 DM subjects from the Atherosclerosis Risk in Communities study (ARIC) (9). This cohort study found that MSSS and non-glucose MSSS at baseline were associated with incident CVD HR 1.29 (95% CI 1.21–1.39; p < 0.001) and HR 1.42 (95% CI 1.24–1.62; p < 0.001), respectively. This outcome study explains our better predictive ability of non-glucose MSSS to detect elevated CIMT than the original MSSS.

We did not find studies related to the association between MSSS and subclinical atherosclerosis as a surrogate marker of cardiovascular risk. Gurka et al. showed that MSSS has an excellent predictive performance of cardiovascular risk if glucose is not considered (9) or even when fasting values is replaced for non-fasting values into this model (11). The independent association of non-glucose-
modified MSSS with cardiovascular risk might be explained for a possible weakness of glycemic status for detecting CIMT. Other risk factors as age, male sex, high-density-lipoprotein cholesterol, and total cholesterol also influence their development (12). However, glycemic parameters as post-prandial glucose (13) and glycemic variability are associated as independent risk factors for CIMT (14). The oxidative stress related to glucose fluctuations could explain this association. So glycemic control is an essential therapeutic intervention to decrease the subclinical atherosclerosis process (15).

DM and MS are associated with atherosclerotic findings as coronary calcium content, abdominal aortic calcification, elevated CIMT, and abnormal ankle-brachial index (ABI). These parameters, alone or combined, with greater cardiovascular risk rate (16). CIMT is one of the earliest surrogates of subclinical cardiovascular disease, and its measurement is easy to use even in-office settings, although its interpretation is operator dependent. Additionally, identifying biomarkers with the ability to predict early structural change, such as CIMT, should be an essential tool for modifying the atherosclerosis process’s natural history as a primary prevention strategy for CVD (17–21).

As a weakness, the study stopped due to the SARS CoV 2 pandemic, and the original sample size did not complete, although the trend would not change in light of the results. Another limitation was that cardiovascular disease background was referred for the subjects without any assessment to rule out subclinical coronary disease. We selected the subjects by non-random sampling from a reference hospital and a primary care center and did not extrapolate beyond the study population. Finally, the small number of males and a wide age range could miss estimating the true prevalence of altered CIMT. As a strength, we evaluated the carotid intima-media thickness with the appropriate technique by on a high-resolution ultrasound and a trained operator.

5. Conclusions

Our results show that non-glucose modified MSSS had the greatest accuracy for detecting CIMT compared with MS-ATP III, MS-harmonizing criteria, and original MSSS. Further studies are necessary to evaluate ultrasonography’s clinical utility as an early intervention to reduce the risk of CIMT progression. Also, to evaluate the role of metabolic syndrome in the development of subclinical atherosclerosis.

Declarations

Ethics approval and consent to participate:

This study have been performed in accordance with the Declaration of Helsinki and it had been approved by an institutional ethics committee of Edgardo Rebagliati Martins Hospital.

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Informed consent to participate in the study was obtained from participants. The informed consent document was approved by the institutional ethics committee.

**Consent for publication:**

Not applicable for that section.

**Availability of data and materials:**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:**

The authors declare to have no compelling interests with this article.

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**Authors' contributions:**

All authors designed the study and collected the data. ATG, DU, and LMT recollected information. MYA performed statistical analyses. ATG and MYA participated in the interpretation of the results. MYA and ATG performed in the writing of the manuscript. All authors approved the final version of the manuscript.

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