Statin indication according to the 2019 World Health Organization cardiovascular disease risk charts and carotid ultrasound in Mexican mestizo rheumatoid arthritis patients

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Abstract

Background: We aimed to assess the concordance of recommendation for initiating statin therapy according to the 2019 World Health Organization (WHO) cardiovascular disease (CVD) risk charts and to the presence of carotid plaque (CP) identified with carotid ultrasound in Mexican mestizo rheumatoid arthritis (RA) patients, and to determine the proportion of patients reclassified to a high cardiovascular risk after the carotid ultrasound was performed.

Methods: This was a cross-sectional study nested of a RA patients’ cohort. A total of 157 Mexican mestizo RA patients were included. The cardiovascular evaluation was performed using the 2019 WHO CVD risk charts (laboratory-based model) for the Central Latin America region. A carotid ultrasound was performed in all patients. The indication to start statin therapy was considered if the patient was classified as high risk, moderate risk if > 40 years with total cholesterol (TC) > 200 mg/dl or LDL-C > 120 mg/dl, and low risk if > 40 years with TC > 300 mg/dl, according to the WHO CVD risk chart or if the patient had carotid plaque (CP). Cohen’s kappa (k) coefficient was used to evaluate the concordance between statin therapy initiation.

Results: Initiation of statin therapy was considered in 49 (31.2%) patients according to the 2019 WHO CVD risk charts and 49 (31.2%) patients by the presence of CP. Cardiovascular risk reclassification by the presence of CP was observed in 29 (18.9%) patients. A slight agreement (k = 0.140) was observed when comparing statin therapy recommendations between 2019 WHO CVD risk charts and the presence of CP.

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Conclusion: The WHO CVD risk charts failed to identify a large proportion of patients with subclinical atherosclerosis detected by the carotid ultrasound and the concordance between both methods was poor. Therefore, carotid ultrasound should be considered in the cardiovascular evaluation of RA patients.

Keywords: Rheumatoid arthritis, Cardiovascular risk, Carotid atherosclerosis, Ultrasound imaging

Introduction
Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease that affects up to 1% of the world adult population and 1.6% of the Mexican population [1, 2]. Cardiovascular disease (CVD) is the most common cause of death of RA patients due to an accelerated process of atherosclerosis and the elevation of proinflammatory cytokines that contribute to endothelial and myocardial damage [2, 3].

Cardiovascular (CV) risk algorithms underestimate the actual risk in Hispanic RA patients [4]. The carotid ultrasound is a useful diagnostic tool to detect subclinical atherosclerosis, which carries high risk of developing a CV event. In previous studies patients with RA initially considered as low or moderate risk according to CV risk algorithms were reclassified to a higher risk category, considering disease activity as an important factor for this reclassification [5].

The 2015/2016 update of the European League Against Rheumatism (EULAR) recommendations for CVD risk management recommend an assessment at least once every five years for all patients with inflammatory joint diseases, including RA. It also recommends a 1.5 multiplication factor for RA patients if the disease is not considered in the algorithm [6]. However, no specific CV risk algorithm had been designed for the Hispanic population until the World Health Organization (WHO) published the CVD risk charts for twenty-one world regions in 2019, including a chart that specifically considers the Hispanic population [7].

Hispanic population, in general, has increased incidence of traditional CV risk factors, such as obesity, type 2 diabetes mellitus (T2DM), hypertension (HTN), and dyslipidemia, due to behavioral, genetic, and environmental factors that independently impact the risk profile of this population [8]. For this reason, a specifically designed algorithm for Hispanic people should improve CV risk stratification, which is necessary to provide timely treatment to prevent a CV event.

According to the 2016 guidelines of the European Society of Cardiology, the presence of CP poses a very high risk for CV events, and the initiation of statin therapy is recommended [9]. Therefore, we aimed to assess the concordance of recommendation for initiating statin therapy according to the 2019 WHO CVD risk charts and the presence of carotid plaque (CP) identified with carotid ultrasound in Mexican mestizo RA patients, and to determine the proportion of patients reclassified to a high CV risk after the carotid ultrasound was performed.

Material and methods
Patients
This cross-sectional study was performed nested of a RA patients’ cohort from an outpatient Cardio-Rheumatology clinic of a tertiary-care hospital in Monterrey, Mexico. We recruited Mexican mestizo RA patients aged 40–75 years, who fulfilled the 2010 American College of Rheumatology/EULAR (ACR/EULAR) criteria for RA. Mexican mestizo was defined as individuals born in Mexico with a Spanish-derived last name and Mexican ancestry belonging to a third-generation family [10]. Patients with previous CV events (myocardial infarction, stroke, or peripheral artery disease), cancer, overlap syndrome, or pregnancy were excluded.

The Research and Ethics committee of our institution approved this study with registration number MI14-006. The study was conducted following the ethical standards outlined in the Declaration of Helsinki and its subsequent amendments. All study subjects provided verbal informed consent before their inclusion.

A medical history and physical examination were performed during the first visit. Demographic and clinical characteristics were collected, and anthropometric measures, such as weight, height, and body mass index (BMI), were obtained. Blood pressure was measured after a 15-min rest on the left arm of all patients. Disease characteristics included disease duration, current medication with glucocorticoids, and/or disease-modifying antirheumatic drugs (DMARD) (synthetic and/or biological). Disease activity was evaluated by the Disease Activity Score 28-joints C-reactive protein (DAS28-CRP), considering remission <2.5; low disease activity 2.5–3.19; moderate disease activity 3.2–5.09; and high disease activity >5.1 [11].

A blood sample was drawn for lipid profile (total cholesterol [TC], low density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C]), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibodies (considering a value >20.0 U/mL and >5 U/mL as seropositive by ELISA, respectively).
Carotid ultrasound
A high-resolution B-mode carotid ultrasound was performed with a linear 10-MHz transducer and a Logiq E9 ultrasound system (GE Healthcare, Milwaukee, WI, USA) by a certified radiologist. The subject was placed in a supine position according to the American Society of Echocardiography guidelines. CP was defined as a focal narrowing ≥ 0.5 mm of the surrounding lumen or a carotid intima-media thickness ≥ 1.2 mm [12].

2019 WHO CVD risk charts
The CV risk evaluation was performed by a certified cardiologist, blinded to the carotid ultrasound results, using the 2019 WHO CVD risk charts for the Central Latin America region, which considers Mexico. Charts are available to estimate CV risk using two modalities: a laboratory-based model including age (40–75 years), gender, smoking status, systolic blood pressure, history of diabetes, and TC (140–300 mg/dL), and a non-laboratory-based model in which BMI replaces TC. The laboratory-based model was used because it has the greatest discrimination, according to the recommendation [7]. The score was multiplied by 1.5 as stated in the EULAR recommendations of 2015 [6]. Patients were classified into five categories: low risk < 5%; moderate risk 5–10%; high risk 10–20%; very high risk 20–30%; and critical risk > 30%. Indications to start statin therapy by these charts were patients with high, very high or critical CV risk, patients with moderate CV risk older than 40 years with TC > 200 mg/dL or LDL-C > 120 mg/dL, and patients with low CV risk older than 40 years with TC > 300 mg/dL [7]. Subsequently, patients who did not meet these conditions but had CP were reclassified to a high-risk category with the indication of starting statin therapy.

Patients’ selection
At the time this study was performed, our cohort had a total of 490 RA patients recruited. Patients without previous or current statins’ treatment, with a carotid ultrasound performed and necessary data to calculate the CV risk with the 2019 WHO CVD risk charts (age, gender, smoking status, systolic blood pressure, history of diabetes and TC) collected or measured at the time of recruitment, were consecutively included for this study.

Statistical analysis
For quantitative variables the distribution of normality was evaluated using visual (histograms and probability plots) and analytical (Kolmogorov–Smirnov test) methods. A descriptive analysis was done using frequencies (%), mean ± SD, or median (p25–p75), accordingly. Cohen’s kappa (k) coefficient was used to evaluate the concordance between statin therapy initiation according to the 2019 WHO CVD risk charts and the presence of CP. k values were calculated and stratified qualitatively by score (0.00–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.0 almost perfect agreement). The Chi-square test was used for comparisons of qualitative variables. A p value < 0.05 was considered statistically significant. The statistical analysis was performed using SPSS v.25.0 (IBM Corp., Armonk, NY, USA).

Results
A total of 157 RA patients were included for this study. Most patients were women (94.9%) with a mean age of 55.31 ± 9.4 years. Regarding comorbidities, 36 (22.9%) had a diagnosis of dyslipidemia, 54 (34.4%) hypertension, 60 (38.2%) were obese, 25 (15.9%) were diagnosed with T2DM, and 15 (9.6%) were active smokers. The lipid profile showed a mean TC of 177 ± 34.1 mg/dL, a mean LDL-C of 96 ± 29.1 mg/dL, and a median HDL-C of 51.8 (43.9–61.9) mg/dL.

RA patients had a median disease duration of 8.4 (3.7–16.2) years. Mean disease activity was 3.45 ± 1.37 by DAS28-CRP, classifying 50 (31.8%) patients in remission, 20 (12.7%) in low disease activity, 65 (41.4%) in moderate disease activity, and 22 (14.0%) in high disease activity. A total of 99 (63.1%) patients were seropositive for anti-CCP, and 132 (84.1%) for RF. Regarding the pharmacological treatment, 87 (55.4%) were on glucocorticoids therapy, 123 (78.3%) on methotrexate therapy, and only 15 (9.6%) were on biological DMARD (bDMARD) at the moment of the evaluation. Demographic and disease characteristics are shown in Table 1.

When evaluating the CV risk according to the 2019 WHO CVD risk charts, 83 (52.9%) patients were classified as low risk, 39 (24.8%) patients as moderate risk, 32 (20.4%) patients as high risk, 3 (1.9%) patients as very-high risk, and none as critical risk. The initiation of statin therapy was considered in 49 (31.2%) patients according to the 2019 WHO CVD risk charts, 14 (8.9%) of them were classified as moderate risk, 32 (20.4%) as high risk, and 3 (1.9%) as very-high risk.

According to the carotid ultrasound, 49 (31.2%) patients had the indication to start statin therapy, due to the presence of CP (Table 2). CV risk reclassification by the presence of CP was observed in 29 (18.9%) patients. A total of 78 (49.68%) patients had a recommendation for statin therapy initiation by both methods (Table 3). A slight agreement (k = 0.140) was observed when comparing statin therapy recommendations between the 2019 WHO CVD risk charts and the presence of CP.
Table 1 Demographic and disease characteristics of all study subjects

| Variable                                | RA patients (n = 157) |
|-----------------------------------------|----------------------|
| Demographic characteristics             |                      |
| Age (years), mean ± SD                  | 55.3 ± 9.4           |
| Female, n (%)                           | 149 (94.9)           |
| BMI (kg/m²), mean ± SD                  | 29.37 ± 5.68         |
| Systolic blood pressure, mean ± SD      | 123 ± 17             |
| Dyslipidemia, n (%)                     | 36 (22.9)            |
| Hypertension, n (%)                     | 54 (34.4)            |
| Obesity, n (%)                          | 60 (38.2)            |
| T2DM, n (%)                             | 25 (15.9)            |
| Active smokers, n (%)                   | 15 (9.6)             |
| Former smokers, n (%)                   | 19 (12.1)            |
| Antihypertensive treatment, n (%)       | 48 (30.6)            |
| Lipid profile                           |                      |
| Total cholesterol (mg/dl), mean ± SD    | 177.6 ± 34.1         |
| Triglycerides (mg/dl), median (p25–p75) | 128 (92.1–163.8)     |
| LDL-C (mg/dl), mean ± SD                | 96 ± 29.1            |
| HDL-C (mg/dl), median (p25–p75)         | 51.8 (43.9–61.9)     |
| Disease characteristics                 |                      |
| Disease duration (years), median (p25–p75) | 8.4 (3.7–16.2)        |
| DAS28-CRP, mean ± SD                    | 3.45 (± 1.37)        |
| Disease activity classification (DAS28-CRP) |              |
| Remission, n (%)                        | 50 (31.2)            |
| Low, n (%)                              | 20 (12.7)            |
| Moderate, n (%)                         | 65 (41.4)            |
| High, n (%)                             | 22 (14)              |
| HAQ, median (p25–p75)                   | 0.38 (0–1.06)        |
| Positive RF, n (%)                      | 132 (84.1)           |
| Positive anti-CCP, n (%)                | 99 (63.1)            |
| CRP (mg/dl), median (p25–p75)           | 0.81 (0.5–1.25)      |
| ESR (mm/h), median (p25–p75)            | 23 (15–37)           |
| Treatment                               |                      |
| MTX, n (%)                              | 123 (78.3)           |
| Glucocorticoids, n (%)                  | 87 (55.4)            |
| bDMARD, n (%)                           | 15 (9.6)             |

RA rheumatoid arthritis, BMI body mass index, T2DM type 2 diabetes mellitus, LDL-C low-density lipoprotein cholesterol, HDL high-density lipoprotein cholesterol, DAS28-CRP disease activity score using 28 joints and C-reactive protein, HAQ health assessment questionnaire, RF rheumatoid factor, CRP C-reactive protein, ESR erythrocyte sedimentation rate, MTX methotrexate, bDMARD biologic disease-modifying antirheumatic drugs

Table 2 Statin therapy recommendation according to the WHO CVD risk charts and the presence of CP

| RA patients (n = 157) | Patients with CP, n (%) | Patients without CP, n (%) |
|----------------------|-------------------------|---------------------------|
|                      |                         |                           |
| Patients with statin therapy recommendation according to the WHO CVD risk charts | 20 (40.8) | 29 (26.9) |
| Patients without statin therapy recommendation according to the WHO CVD risk charts | 29 (59.2) | 79 (73.1) |

WHO World Health Organization, CVD cardiovascular disease, CP carotid plaque

Table 3 Patient with statin therapy recommendation

| Recommendation | RA patients (n = 157) |
|----------------|----------------------|
| 2019 WHO CVD risk charts, n (%) | 49 (31.2) |
| Carotid ultrasound, n (%) | 49 (31.2) |
| Reclassification, n (%) | 29 (18.9) |
| Total patients with statin therapy recommendation by any method, n (%) | 78 (49.6) |

RA rheumatoid arthritis, WHO World Health Organization, CVD cardiovascular disease

We found that most reclassified patients belonged to the moderate-high disease activity category, however the difference was not significant (62.1% vs. 37.9%, p = 0.425).

Discussion

We found a slight agreement between the 2019 WHO CVD risk charts and the presence of CP, indicating the initiation of statin therapy in the same number of patients; however, almost one-fifth of our population was reclassified to a high-risk category after the carotid ultrasound. Therefore, even though the same number of patients had a recommendation for the initiation of statin therapy, there was still a significant number of patients being subclassified by this algorithm. These results differ from those observed in a previous study performed in Mexican mestizo RA patients, where a moderate agreement between the 2013 ACC/AHA algorithm and the presence of CP was found regarding the start of statin therapy [13].

The underestimation of the CV risk of these patients could be attributed to the fact that the 2019 WHO CVD risk charts do not include other traditional CV risk factors such as history of hypertension, HDL-C, LDL-C, diastolic blood pressure, and especially the BMI, considering that the Mexican population has the highest rates of obesity and overweight, according to the last national survey, which are modifiable risk factors that play an
important role in CVD development [14, 15]. On the other hand, Cuende et al. [16] state that inflammatory diseases, particularly RA, have an accelerated atherosclerosis process that inflammation can influence. Data from the literature suggest a central role of the immune system in the pathogenesis of CV disease, linking proinflammatory cytokines involved in RA with increased atherogenesis. Various mechanisms beyond traditional CV risk factors contribute to this risk, including inflammatory mediators, oxidative stress, endothelial dysfunction, and unique quantitative and qualitative lipid alterations [17, 18]. Therefore, inflammatory markers are criteria that should be considered when evaluating the CV risk of these patients.

Enormous efforts have been made to find a tool that estimates the real CV risk in patients with RA. The response has not yet been favorable even when new options have been proposed, such as the expanded risk score for RA (ERS-RA), that showed not having a better discrimination than non-specific calculators, in multiple studies, such as a cohort of seven countries, including Mexico [19, 20].

As mentioned above, the EULAR recommends that CV risk algorithms that do not include RA as a parameter should multiply the result by 1.5 to improve the risk estimation [6]. A systematic review of five studies carried out with Mexican population demonstrated an overall prevalence of 21% for CVD in RA patients [21]. In addition, a cohort of Hispanic patients with early RA, demonstrated that there was a distinctive pattern for CV risk factors during the follow-up, with dyslipidemia and obesity being the factors with the highest incidence; therefore, it could be a mistake to try to apply international recommendations in this population [22]. Our study showed that despite applying the EULAR recommendations and multiplying the value provided by the calculator, the estimation of CV risk was still insufficient since 18.9% of the patients were reclassified by carotid ultrasound.

The importance of these findings is that early treatment with statins could be beneficial in the primary prevention of a CV event [23–25]. What is shown in this study is that even when using a specific algorithm for Mexican population, the performance of a carotid ultrasound remains essential for CV risk evaluation of Mexican mestizo RA patients, because this allows the identification of patients subclassified with the algorithm.

Some strengths of this study should be highlighted. To our knowledge, this is the first study to compare the CV risk evaluation by carotid ultrasound and a CV risk algorithm that includes Mexican mestizo population, such as the 2019 WHO CVD risk charts, in RA patients. Additionally, none of the patients had previous statin treatment. Among the limitations of this study are the number of patients included and the single-center cross-sectional design of the study.

Conclusions

The WHO CVD risk charts failed to identify a large proportion of patients with subclinical atherosclerosis detected by the carotid ultrasound and the concordance between both methods was poor. Therefore, carotid ultrasound should be considered in the CV evaluation of RA patients. Prospective studies that include RA patients and controls are still needed to evaluate the true effectiveness of the WHO CVD risk charts to predict CV events at 10 years. Combining both methods could be a useful algorithm for a comprehensive evaluation and, above all, for identifying the maximum number of patients who would benefit from early intervention with statins, emphasizing that a carotid ultrasound cannot be omitted.

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Authors’ contributions

All authors had access to the data and a role in writing the manuscript. DAG-D, IJC-P, JRA-L, NG-J, ABR-R and JAC-dlG contributed to the study conception and design. JL-A and AM-G performed the statistics. SL-P and JNC-T analyzed and interpreted the data. NG-J, ABR-R, JL-A, AM-G and JAC-dlG drafted the first manuscript while all authors revised and approved the final manuscript.

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Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional research and ethics committee of the University-Hospital “Dr. Jose E. Gonzalez” from the Universidad Autonoma de Nuevo Leon, with registration number MI14-006 and was therefore conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and its subsequent amendments. Verbal informed consent was obtained before the inclusion.

Consent for publication

Not required.

Competing interests

None of the authors of this study has any financial interest or conflict with industries or parties.

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